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Formulation and Evaluation of the Tramadol HCl Oral Disintegrating Film by Using The Co-processed Superdisntegrants

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ABSTRACT

Oral fast disintegrating films (OFDF) is an emerging technology brings out "formulations taken without water" with quick onset of action and improved patient compliance. The present aim of study is to enhance the dissolution rate of the dosage form by using the different superdisintegrants and co-processed superdisintegrants. The films were prepared by solvent casting method using hydrophilic polymers that rapidly dissolves on the tongue or buccal cavity, delivering the drug to the systemic circulation. The polymer was used HPMC E15, PEG 6000 as plasticizer, citric acid as the saliva stimulating agent, sucrose as the sweetening agents and sodium starch glycolate, crosscarmelose sodium and crospovidone as the superdisintegrants and tween 80 as surfactant . The FTIR reports suggest that drug and excipients were compatible. These oral disintegrating films were evaluated for various evaluation parameters. The *in-vitro* dissolution studies were conducted as per USP II with sinker. There were three ODFs prepared by using different types of the superdisintegrants, two were prepared by using the co-processed superdisintegrants and one was without any superdisintegrants. Among all formulation, the F6 shown the better *in-vitro* drug release profile which was prepared by using co-procesed superdisintegrants. It can be concluded that the co-processed superdisintegrants enhances the dissolution rate by comparing with other formulation.

Keywords: HPMC E15, PEG 6000, SSG, CCS, Crospovidone, co-processed superdisintegrants, Tramadol hydrochloride.

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INTRODUCTION

An alternative to conventional dosage forms for paediatric and geriatric patients who experience difficulties in swallowing traditional oral solid dosage forms formulate the fast dissolving tablets by using superdisintigrants and hydrophilic ingredients which has the higher bioavailability, quick action and most patient compliance. To eliminate the drawbacks of fast dissolving tablet a fast dissolving film can be placed. Fast dissolving films are very similar to ultra-thin strip of postage stamp in their shape, size and thickness. Fast dissolving films are formulated using polymers, active pharmaceutical ingredients (API), plasticizers, saliva stimulating agents, sweeteners, flavours, preservatives and colours. Fast dissolving film is simply placed on the patient's tongue or any oral mucosal tissue, instantly wet by saliva the film rapidly hydrates and adheres onto the site of application. It then rapidly disintegrates and dissolves to release the medication for oral-mucosal absorption and modification in formula will maintain the quick-dissolution of API and allow for gastrointestinal absorption when swallowed[1]. Tramadol HCl is a centrally acting synthetic analgesic that possesses two complementary mechanisms of action at therapeutic doses. The Tramadol binds weakly to μ- and δ-opioid receptors and inhibits the reuptake of serotonin and norepinephrine[2]. A major metabolite of tramadol, O-desmethyl tramadol, has an approximately 200 fold higher affinity for opioid receptors than the parent compound. Tramadol is used to treat postoperative, dental, cancer and acute musculosketetal pain and as an adjuvant to nonsteroidal antiinflammatory drug (NSAID) therapy in patients with osteoarthritis. Also, it is recommended in postsurgical pain when patient is hospitalized. The Tramadol HCl is the 5HT and NA uptake blocker, weak μ agonist, avoid with MAO inhibitor[3]. HPMC E15 is primarily used as binder, in film coating and as an extended release tablet matrix. It is also known as Hypromellose. HPMC E15 stands for HPMC of 15cps viscosity[4]. PEG 600 as plasticizer which improve the mechanical properties such as tensile strength and percent elongation[5]. Tween 80 is a surfactant which plays a vital role as dispersing, wetting and solubilising agent thus enabling films to disintegrate within seconds releasing the incorporated drug[5]. Peppermint oil is the flavouring agent which improves nauseating taste of incorporated drug[5]. Sucrose is the sweetening agent designed to disintegrate or dissolve in oral cavity. Citric acid is the saliva stimulating agent which are generally acidic in nature stimulating the production of saliva in buccal cavity, consequently, promoting the disintegrating of ODFs[6]. The SSG, CSS, crospovidone are the superdistegrants, they releases the drug in oral mucosa within the second of time.

MATERIALS AND METHOD

Tramadol HCL was obtained as a gift sample from Dr. Reddy's laboratories, Hyderabad, HPMC E15, PEG 6000, Crosscarmellose sodium, Sodium starch glycolate, Crospovidone were procured from Microlabs Bangalore. All the other chemicals used were of analytical grade. Polymer films were prepared by solvent casting method according to the formula Table 1. Propylene glycol 6000 (PEG) used as a plasticizer, was dissolved into small quantity of purified water. Polymer was dissolved in the plasticized solution and this solution was deaerated by sonication. Film was casted on plastic Petri plate. Film was dried in hot air oven for suitable period of time at temperature of 60º C. The concentration of polymer which formed smooth, non-sticky, fast disintegrating and easily peelable film was selected for formulation of drug loaded film. The formulation was shown in table 1.

Formulation of drug loaded films

Drug loaded films were also prepared by solvent casting method. The 438 mg of Tramadol hydrochloride was incorporated into 2×2 cm^2 area of film. Drug added into the film forming solution was calculated by considering total amount of solution to be poured in order to obtain films with desired thickness on a specific surface area of the petri plate. Solution was then casted in to a Petri dish having area of 70cm^2 and 1.3cm wall height. Petri dish was kept in hot air oven for 12 hr at 50ºC[7]

Procedure for preparation of the co-processed superdisintegrants[8]

1) Preparation of sodium starch glycolate and crospovidone as co-processed superdisintegrants

The co-processed superdisintegrants were prepared by solvent evaporation method.

↓

Weighed quantity of sodium starch glycolate + crospovidone were mixed (in the ratio of 1:1)

↓

Above mixed quantity added to the 10 ml of ethanol

↓

Mixed thoroughly & stirring was continued till most the ethanol evaporated

↓

The wet coherent mass was granulated through 44 mesh sieve

↓

Wet granule were dried in a hot air oven at 60^0 C for 20 min

↓

Dried granule were sifted through 44 mesh sieve and stored in airtight container for further use.

2) Preparation of Croscarmellose sodium and crospovidone as co-processed superdisintegrants

Procedure as above protocol

The co-processed superdisintegrants were prepared by solvent evaporation method.

↓

Weighed quantity of Croscarmellose sodium + crospovidone were mixed (in the ratio of 1:1)

↓

Above mixed quantity added to the 10 ml of ethanol

↓

Mixed thoroughly & stirring was continued till most the ethanol evaporated

↓

The wet coherent mass was granulated through 44 mesh sieve

↓

Wet granule were dried in a hot air oven at 60^0 C for 20 min

↓

Dried granule were sifted through 44 mesh sieve and stored in airtight container for further use.

Table 1: Formulation of Oral Disintegration film of Tramadol HCL

Ingredients	F1	F2	F3	F4	F5	F6
Tramadol HCL(mg)	438.00	438.00	438.00	438.00	438.00	438.00
HPMC E15(mg)	197.10	197.10	197.10	197.10	197.10	197.10
PEG 6000(mg)	43.80	43.80	43.80	43.80	43.80	43.80
SUCROSE(mg)	17.52	17.52	17.52	17.52	17.52	17.52
CITRIC ACID(mg)	21.90	21.90	21.90	21.90	21.90	21.90
TWEEN 80	QS	QS	QS	QS	QS	QS
PIPERMINT OIL(mg)	QS	QS	QS	QS	QS	QS
SSG(mg)	-	35.04	-	-	-	-
CROSS PVP(mg)	-	-	-	35.04	-	-
CSS(mg)	-	-	35.04	-	-	-
CROSS PVP+SSG(mg)	-	-	-	-	35.04	-
CROSS PVP+CSS(mg)	-	-	-	-	-	35.04

Quantity of drug was calculated as per the area of Petri dish, so that each film 2×2 cm^2 contained 25 mg of drug.

Dose calculation:

The calculation of the dose depends upon the surface area of Petri dish.

The surface area of Petri dish = 70 cm^2

The dose of Tramadol HCl = 25mg

No. of 4cm^2 (2*2) present in whole plate = 70/4 = 17.5

Each film contains 25 mg of drug.

17.5 no. of film. mg of drug? =17.5*25 = 437.5mg

The amount of drug added in each plate was approximately equal to 438 mg.

Evaluation of ODFs

Thickness measurement[9]

The thickness of each film was measured at five different locations (centre and four corners) using Vernier calliper micrometer.

***In -vitro* disintegration time[10]**

The film size required for dose delivery (2×2 cm^2) was placed in a glass Petri dish containing 10 ml of distilled water. The time required for the film to break was noted as *in-vitro* disintegration time. The test was conducted in triplicates.

Tensile strength[9]

It is the maximum stress applied to a point of a film at which the strip specimen breaks. It is calculated by applied load at rupture divided by the cross section area of the strip as given in the equation:

Tensile strength= Load at failure*100/ strip thickness* strip width

Percentage moisture loss[11]

Percentage moisture loss was also carried to check the integrity of films at dry condition. It is determined by placing the prepared film in desiccators containing anhydrous calcium chloride. After three days, the film was taken and reweighed. The percent moisture loss was calculated using the following formula.

%Moisture loss = Initial weight- Final weight/ Initial weight x 100

Percentage moisture absorption[11]

The percentage moisture absorption test was carried out to ensure physical stability or integrity of films at high humid condition. The films were weighed and placed in a desiccators containing 100 ml of saturated solution of aluminium chloride and 75±5% RH was maintained. After three days the films were taken out and reweighed. The percentage moisture absorption was calculated using the following formula.

%Moisture absorption = Final weight- Initial weight / Initial weight x 100

Folding endurance[12]

The folding endurance of the film was determined by repeatedly folding one film at the same place till it breaks from the one end of the film. The number of times of film could be folded at the same place without breaking was noted which gave the value of the folding endurance.

RESULTS AND DISCUSSION

API Characterization

Physical appearance

The drug was tested for its physical appearance by visual identity. It was found to be white to off-white in colour.

Solubility

Solubility was performed by adding excess quantity of drug to different solvents and buffers. It is freely soluble in water, soluble in buffers of pH 6.8. Concentration was estimated by spectrophotometric method. The solubility shown in table 2.

Table 2: Solubility of the Tramadol hydrochloride

S. no	Solvents	Solubility±SD(mg/ml)
1	Water	2.240±0.08
2	Phosphate buffer 6.5	15.052±0.06
3	Phosphate buffer 6.8	25.256±0.02
4	Chloroform	1.230±0.03

Melting point

The melting point of the drug was determined by open capillary method. The drug was filled in glass capillary tube, which was sealed at one end. The range of temperature from the starting of melting of drug till it completely melted was recorded and was found to be 180^0C.

Analytical methods development for Tramadol HCl

The determination of wave length maximum and standard curve of Tramadol HCL in phosphate buffer of pH 6.8 was carried out by UV-spectrophotometry. The wavelength maximum was found to be 271nm. The calibration was shown by figure 1.

Drug and excipient compatability studies

FTIR studies

The comparison of the IR spectrum revealed that there is no appreciable change in the positions of characteristic absorption bands of groups and bonds. The spectra of these, even though slightly differ in appearance but no change is observed in the positions of the bands in the spectra. This clearly suggests that the drug remains in the same form even in its formulations indicating that there is no interaction between the drug and polymer used for the study. The results were shown in Figure 2-5

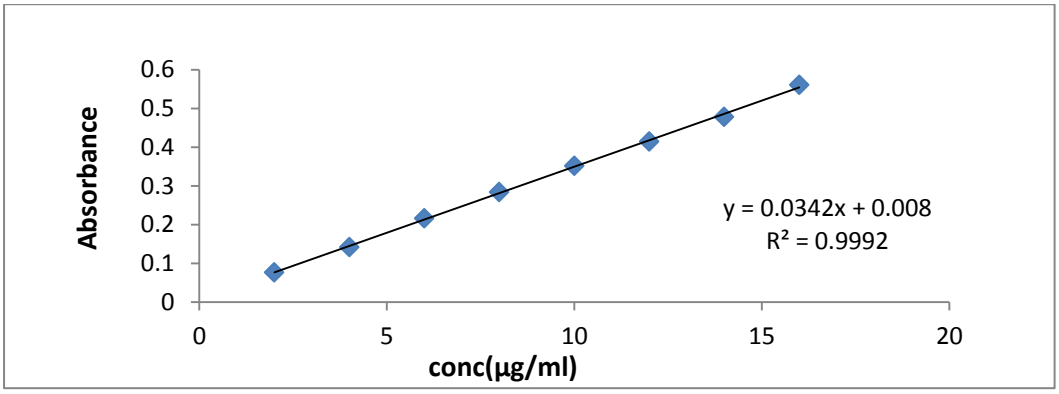


Figure 1: Calibration curve of Tramadol HCL

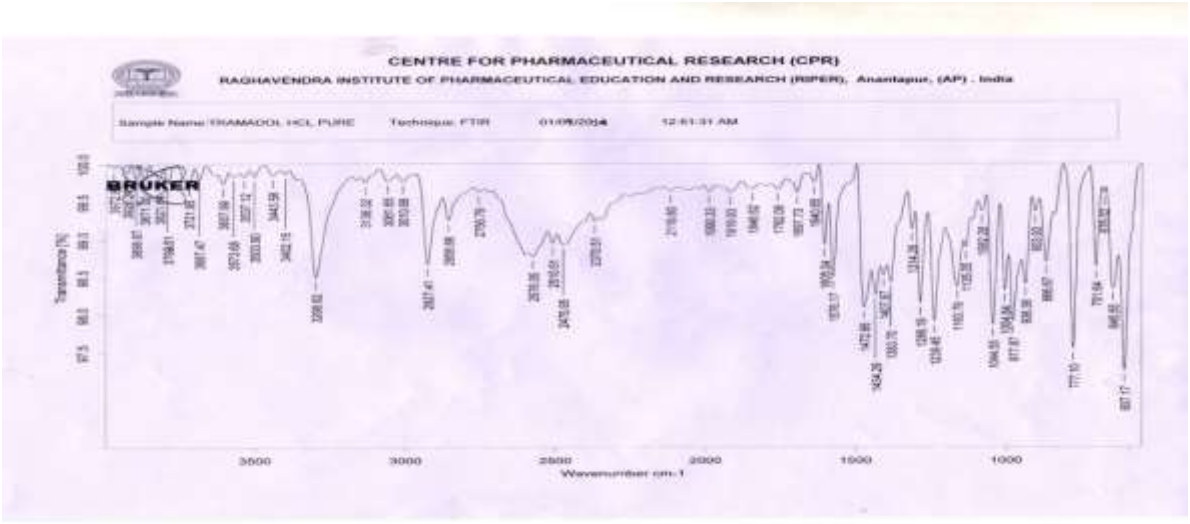


Figure 2 :IR spectrum of Tramadol HCL Pure

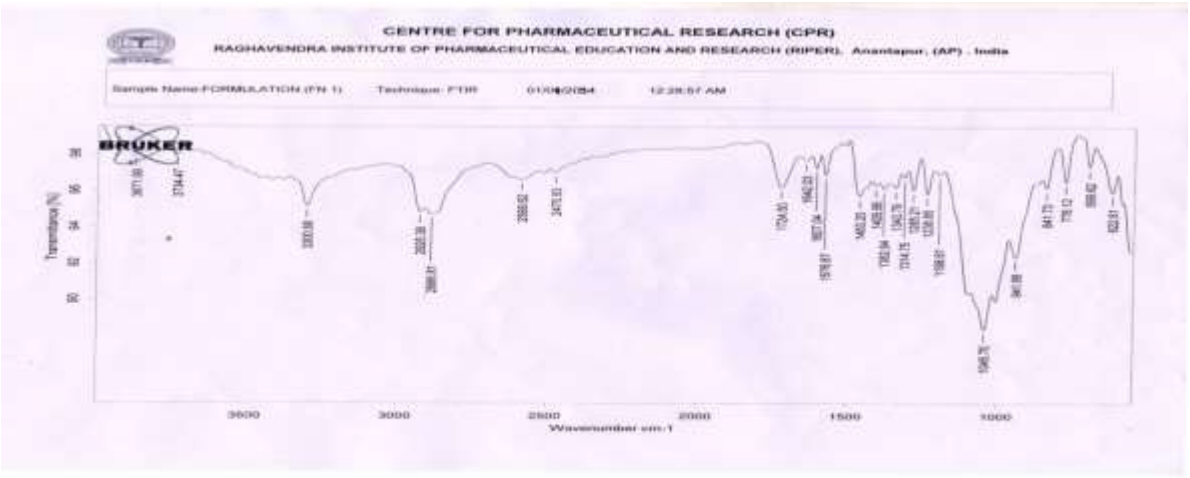


Figure 3: IR spectrum of Formulation (F1) with SSG

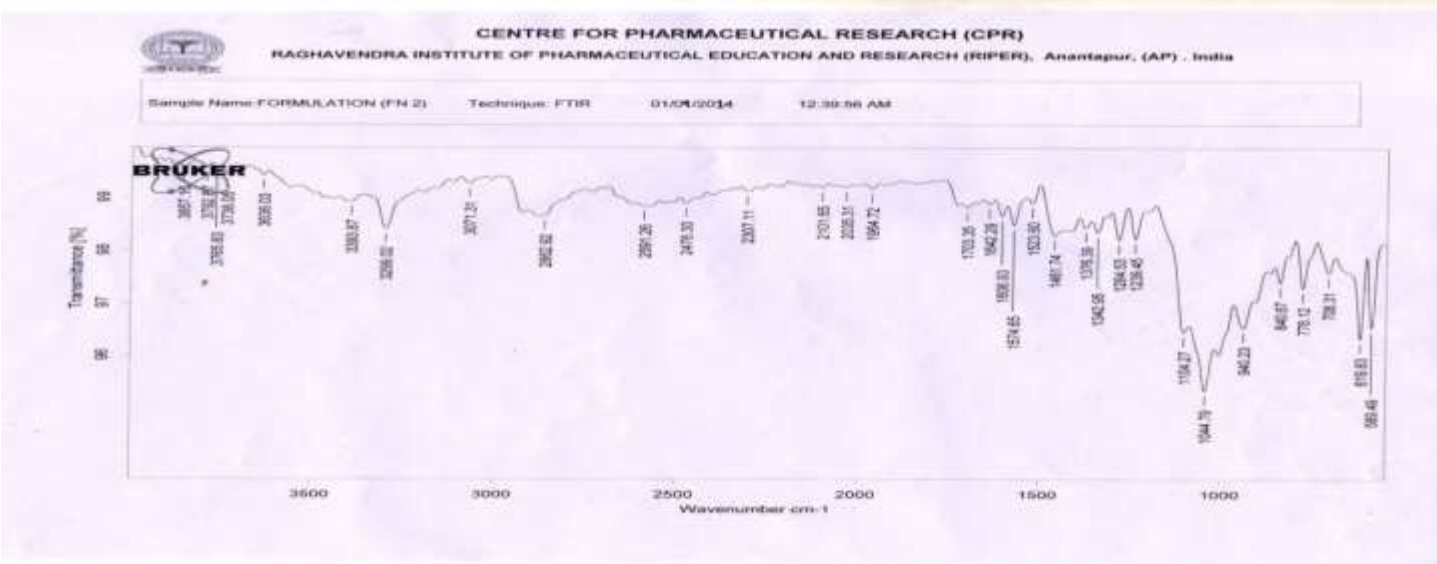


Figure 4: IR spectrum of Formulation (F2) with crospovidone

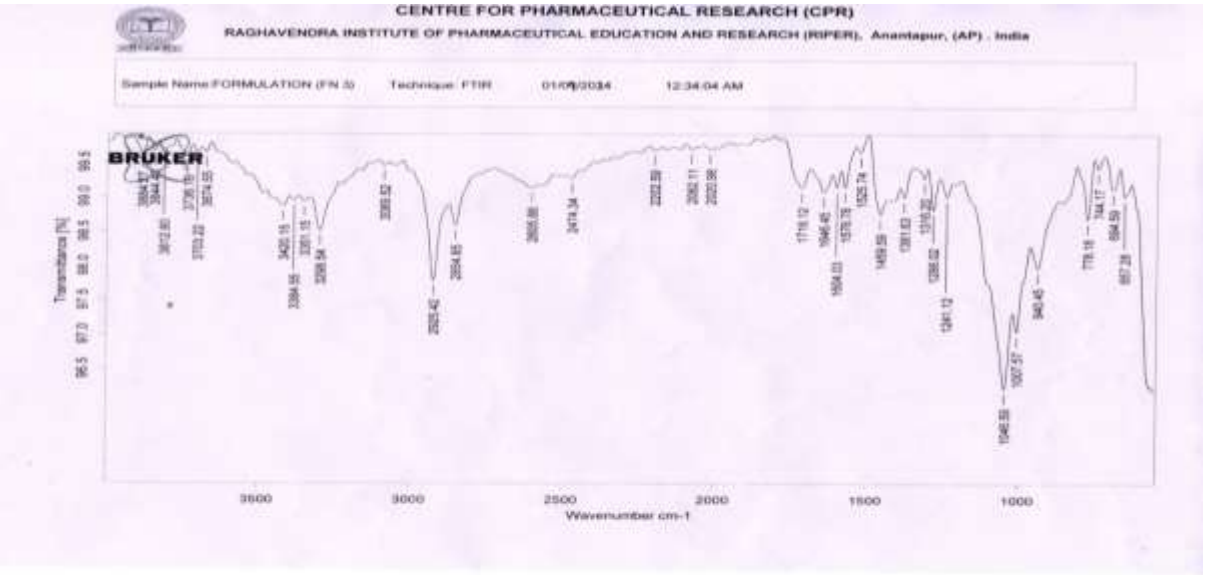


Figure 5: IR spectrum of Formulation (F3) with croscarmellose sodium

Disintegration of oral disintegration film

The different concentrations of oral disintegration film were prepared. Initially investigation was focused on development of polymer films with good peel ability from substrate, uniform appearance, non-tackiness, optimum flexibility, in-vitro disintegration time of less than 30 seconds. There were different types of the super disintegrants used in the formulation; they were sodium starch glycollate, cross povidone, croscarmellose sodium, co-processed superdisintegrants. The results were shown on table 3

Table 3: Evaluation of Oral Disintegration Film of Tramadol HCL

Formulation	F1	F2	F3	F4	F5	F6
Appearance	Smooth surface and transparent	Smooth surface and transparent	Smooth surface and transparent	Smooth surface and translucent	Smooth surface and translucent	Smooth surface and translucent
Tack test	Non tacky	Non tacky	Non tacky	Non tacky	Non tacky	Non tacky
Thickness (mm)	0.210mm	0.205 mm	0.148 mm	0.214 mm	0.213mm	0.209mm
Disintegration time(seconds)	1min11sec	52 sec	48sec	35 sec	29 sec	27 sec
Folding endurance	279	280	274	265	264	260
Tensile strength Kg/cm^2	1.90	1.86	1.50	1.31	1.30	1.28
% Drug content	90.99	96.72	97.85	99.60	98.90	99.80
Percentage moisture loss	2.70	2.69	1.67	1.45	1.48	1.39
% moisture absorption	4.82	4.80	4.41	2.21	2.20	2.15

***In-vitro* drug release**

The *in-vitro* dissolution test was performed using the USP dissolution apparatus II (Paddle with sinker). The dissolution studies were carried out at 37±0.5° C with stirring speed of 75 rpm in 900 ml of Phosphate buffer of pH 6.8. The film size required for dose delivery (2×2 cm^2) was used. The 5ml of dissolution media was collected at time intervals and were performed for 3minutes and replaced with equal volumes of Phosphate buffer of pH 6.8. The collected samples were filtered through 0.45µm membrane filter and the concentration of the dissolved Tramadol HCl was determined using UV-Visible spectrophotometer at 271 nm. The results were presented as an average of three such concentrations. The result was shown in table 4.The comparisons of the *in-vitro* drug release profile of the different formulation were shown by figure 6.

Table 4: *In-vitro* drug release of ODFs of Tramadol HCL

Time(Sec)	Cumulative drug release (n =3)					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
30	38.521±0.0036	50.563±0.0020	52.527±0.0032	54.654±0.0041	55.653±0.0050	56.752±0.0047
60	43.320±0.0037	58.009±0.0040	61.445±.0030	63.436±0.0060	64.562±0.0051	65.564±0.0045
90	52.361±0.0045	64.881±00041	61.545±0.0049	74.345±0.0056	76.456±0.0052	77.565±0.0045
120	59.230±0.0046	74.399±0.0050	82.827±00036	85.009±0.0060	86.035±0.0045	87.235±0.0065
150	65.341±0.0032	84.627±0.0055	87.136±.0041	90.409±0.0045	91.450±0.0032	91.564±0.0051
180	70.120±0.0043	86.627±0.0055	95.809±0.0041	98.820±0.0032	98.990±0.0050	99.890±0.0028

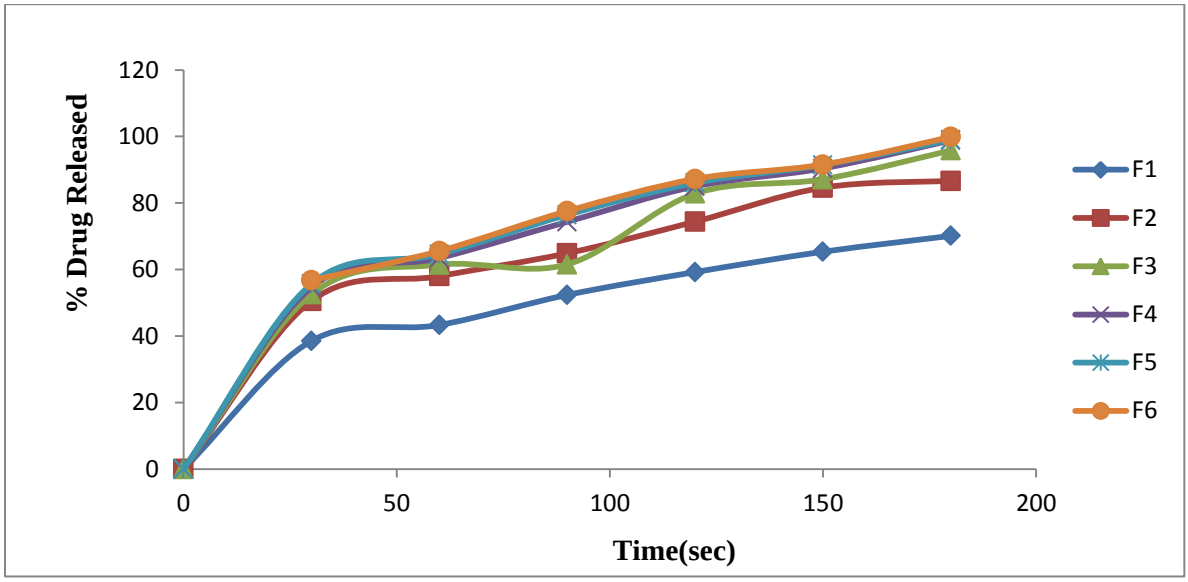
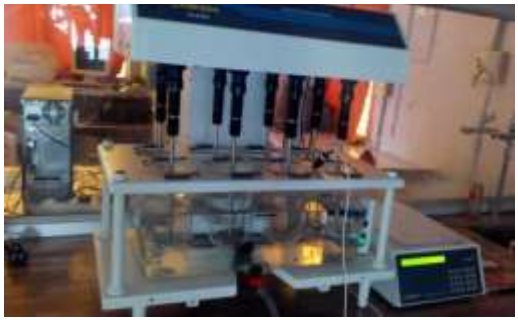


Figure 6: *In-vitro* drug release profile of different formulation

RESULTS AND DISCUSSION

By performimg the *in-vitro* dissolution, the F6 was found the best formulation which containing the crospovidone and crosscarmelose sodium co-processed superdisintegrants and the dissolution result were shown by table no.4.The other F2, F3, F4, F5,shown the less in-vitro drug release which were containing starch glycolate, crospovidone sodium, croscarmeloseodium, co-processed super disintegrants respectively. The disintegration test shown that the F6 disintegrate at 27sec, F5 disuntegrates at 29sec, F4 disintegrates at 35sec, F3 at 48sec and F2 at 52 sec and F1disnitegrates at 1min and 11 sec which were shown in table 3. The tack test shown that the all ODFs were non-tacky which are shown in table 3. The thickness was measured by the vernier calliper the results were shown in the table 3. The folding endurance tests were performed and result shown by table no.3. The tensile strength was performed and result shown by table 3. The percentage drug content assay performed and result were shown in the table 3. The percentage moisture loss test was performed and result was shown in table 3. The percentage moisture absorption was performed result shown by table 3.



Picture : Dissolution assembly

Picture : Sinker

Picture: Paddle and basket

CONCLUSION

The Tramadol HCL oral disintegration film was prepared by solvent casting method by dissolving the water soluble polymer HPMC E15 in water and by dissolving the drug in water. The PEG 6000 used as the plasticizer, citric acid as saliva stimulating agent, sucrose as the sweetening agent, sodium starch glycolate, crosscarmellose sodium and cross povidone and co-processedsuper disintegrating agent. The ODFs were evaluated for the preformulation studies i.e. FTIR which showed no significant changes. Hence the drug and excipients were compatible. The solubility of dissolution rate of Tramadol HCl can be successfully improved by formulating the ODFs. Among the different formulation of the ODFs, the F6 contains the co-processed superdisintegrant that showed the increase in dissolution rate when compared with other formulation. The F1shown very slow in-vitro drug release profile because it did not contain any types of the superdisintegrants. Hence the co-processed superdisintegrant enhances the dissolution rate of drug like Tramadol HCl when compared with sodium starch glycolate, croscarmellose sodium, and crospovidone pyrollidone.

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