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FORMULATION AND EVALUATION OF TRAMADOL HYDROCHLORIDE ORAL THIN FILMS

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ABSTRACT: Oral films are a novel approach for the development of orally disintegrating dosage forms. They are thin, elegant in appearance and can be made into various sizes and shapes like rectangular or circular. The strips may be flexible or brittle, opaque or transparent. Oral films are made up of various hydrophilic and hydrophobic polymers to provide rapid disintegration on the tongue without the need for water. The aim of the present study is to develop fast dissolving films of tramadol Hydrochloride by enhancing drug dissolution in the oral cavity. The development of the films decreases the analgesic effect in less time and increases the patient's compliance. Tramadol HCl films were prepared using Hydroxy propyl methyl cellulose-E5, Hydroxy propyl methyl cellulose-E6, Hydroxy propyl methyl cellulose-E15 and sodium alginate as polymers. Therefore the prepared films were evaluated for various parameters like physical appearance and surface texture of the film, thickness of the film, folding endurance, moisture uptake, uniformity of weight and drug content, swelling index, *in vitro* disintegration studies, and *in vitro* dissolution studies. Stability studies were also performed. Though all the formulations equally passed the evaluation parameters, it is concluded that oral thin films containing 400 mg of sodium alginate as the polymer because of better dissolution profile.

INTRODUCTION: Since the past few decades there has been a tremendous change in designing various drug delivery systems to achieve rapid onset of action¹. To overcome the limitations of oral dosage forms like tablets and capsules, oral thin films have been developed². These are ultra thin postal stamp sized films which are prepared using hydrophilic polymers with drug and other pharmaceutical excipients³. This delivery system consists of a thin film, which is simply placed on the patient's tongue or mucosal tissue and instantly gets wet by saliva to dissolve the film rapidly⁴.

Most of the drug is swallowed orally with the saliva and the absorption of drug takes place in the gastro-intestinal tract. These are also known as quick disintegrating, orally disintegrating, rapidly disintegrating, mouth dissolving or melt in mouth dosage forms⁵. They offer advantages such as administration without water, ease of swallowing, rapid onset of action and convenience of dosing⁶. The fast dissolving films were prepared using different sweeteners and flavours to improve patient compliance⁷. Tramadol hydrochloride is a centrally-acting synthetic opioid analgesic binding to specific opioid receptors. The main objective of the present study is to develop fast dissolving oral films with rapid dissolution of drug and absorption which may produce the rapid onset of action.

MATERIALS AND METHODS:

Materials: Tramadol HCl (SD fine chemicals Pvt. Ltd.,) Poly ethylene glycol 400 (Creative organics),

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Aspartame (Loba chemicals Pvt. Ltd.), Hydroxy propyl methyl cellulose-E5 (SD fine chemicals Pvt. Ltd.), Hydroxy propyl methyl cellulose –E6 (SD fine chemicals Pvt. Ltd.), Hydroxy propyl methyl cellulose –E15 (SD fine chemicals Pvt. Ltd.), Sodium alginate (Creative organics), Peppermint oil (Creative organics).

Methods:

Characterization of Tramadol HCl:

Solubility of Tramadol HCl: The tramadol has aqueous solubility. The solubility was determined in distilled water and phosphate buffer pH 6.8.

Melting Point Determination: The melting point of tramadol HCl was determined by capillary tube method. Fine powder of the drug was filled into a glass capillary tube which was previously sealed at one end. The capillary tube was tied to a thermometer and subjected to increasing temperatures. Therefore the temperature at which tramadol melts was recorded.

Ultraviolet Spectroscopy: The samples were subjected to UV spectrophotometric analysis and were scanned for absorption maxima (λ_{max}) in the range of 200 - 400 nm using UV spectrophotometer in an appropriate medium. The obtained data was compared with that of reference values in literature ⁸.

Compatibility Studies: FTIR study was carried out to check the compatibility of drug with polymers. Infrared spectrum of tramadol HCl was determined on Fourier Transform Infrared spectrophotometer using KBr dispersion method. The baseline correlation was done using dried potassium bromide. Then the spectrum of dried mixture of drug and potassium bromide was run followed by drug with various polymers by using FTIR spectrophotometer. The range of wavelength was between 400 - 4000 cm^{-1} . ⁹

Formulation of Placebo Films: Polymers of single or in combination were accurately weighed and dissolved in respective solvent and then casted in a petridish with mercury as the plain surface. The films were allowed to dry overnight at room temperature.

Preparation of Fast Dissolving Oral Film of Tramadol Hydrochloride: Oral fast dissolving film was prepared by solvent casting method. Aqueous solution I was prepared by dissolving film forming polymer, in specific proportion of distilled water and allowed to stir for 3 h and kept aside for 1 h to remove all the entrapped air bubbles. Aqueous solution II was prepared by dissolving the pure drug, sweetener, and plasticizer in specific proportion of distilled water. The aqueous solution I and II were mixed and stirred for 1 h.

The solutions were cast on to 64 cm^2 glass plate and dried in the oven at 45 °C for 12 h. The film was carefully removed from surface of glass plate and cut according to required size for testing (2 cm length, 2 cm width). The samples were stored in glass container maintained at a temperature of 30°C and relative humidity 60% \pm 5% until further analysis.

Calculation of Dose for Tramadol hydrochloride: The dose of tramadol HCl is 25 mg. therefore amount of tramadol HCl required in 4 cm^2 (2×2) is 25 mg.

- i. Area of film of 2 cm \times 2 cm.
- ii. Area of glass plate is 64 cm^2 with 8 cm length and 8 cm width.
- iii. Amount of drug present in 64 cm^2 is 400 mg.
- iv. Amount of drug present in 4 cm^2 of film is 25 mg.

TABLE 1: FORMULATION DETAILS OF FAST DISSOLVING FILMS OF TRAMADOL HCl F1-F6

Formulation code	Tramadol HCl (mg)	HPMC-E5 (mg)	HPMC-E6 (mg)	Peppermint oil (ml)	Aspartame (mg) % w/w of polymer	Poly ethylene glycol400
F1	400	200	-	1	50	1
F2	400	300	-	1	50	1
F3	400	400	-	1	50	1
F4	400	-	200	1	50	1
F5	400	-	300	1	50	1
F6	400	-	400	1	50	1

TABLE 2: FORMULATION DETAILS OF FAST DISSOLVING FILMS OF TRAMADOL HCl F7-F12

Formulation code	Tramadol HCl (mg)	HPMC-E15 (mg)	Sodium alginate (mg)	Peppermint oil (ml)	Aspartame % w/w of polymer	Polyethylene glycol (ml)
F7	400	200	-	1	50	1
F8	400	300	-	1	50	1
F9	400	400	-	1	50	1
F10	400	-	200	1	50	1
F11	400	-	300	1	50	1
F12	400	-	400	1	50	1

Evaluation of Fast Dissolving Films: The tramadol hydrochloride films were evaluated for the following properties:

Physical Appearance and Surface Texture of the Film: This parameter was checked by doing visual inspection of films and texture of films was evaluated.

Thickness of Film: Thickness of the film was measured using screw gauge micrometer with a least count of 0.01 mm at different spots of the film. The thickness was measured at five different spots of the film and average was taken.

Folding Endurance: Folding endurance was determined by repeated folding of the whole film at the same place till the film breaks. The number of times the film was folded without breaking was computed as the folding endurance value.

Moisture Uptake: The moisture uptake of the films was determined by exposing them to a temperature of 40 °C and 75% relative humidity for 1 week. The uptake of moisture by the films was calculated with percent increase in weight.

$$\% \text{ moisture uptake} = [\text{Final wt} - \text{Initial wt} / \text{Initial wt}] \times 100$$

Uniformity of Drug Content: This parameter was determined by dissolving one film of dimension 2 × 2 cm containing 25 mg of tramadol hydrochloride by homogenization in 100 ml of pH 6.8 phosphate buffer for 30 min with continuous shaking. From this, 10 ml was diluted to 50 ml using pH 6.8 buffer solutions. The absorbance was measured at 203 nm using an UV spectrometer.

Swelling Index: The studies for swelling index of the film were conducted in pH 6.8 phosphate buffer solution. The film sample (surface area 4 cm²) was weighed and placed in a pre weighed stainless wire sieve of approximately 800 μm mesh. The mesh containing the film sample was submerged into 50

ml of pH 6.8 phosphate buffer solution in a mortar. At definite time interval the stainless steel mesh was removed and excess moisture was removed carefully by wiping with absorbent tissue and reweighed. Increase in weight of the film was determined at regular time intervals until a constant weight was observed.

The degree of swelling was calculated using the formula:

$$SI = (W_t - W_o) / W_o$$

Where SI is the swelling index; W_t is the weight of the film at time t; W_o is the Weight of film at t = 0.

Uniformity of Weight: The weight of the prepared films was determined using digital balance and the average weight of the all the films were calculated.

In vitro Disintegration Study: The *in-vitro* disintegration of the fast dissolving oral film was determined using disintegration test apparatus Electro lab disintegration tester ED-2L (USP). Place one piece of film in each of the six tubes of the basket. Add the disc to each tube and run the apparatus using 900 ml of pH 6.8 phosphate buffer solution as the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute in distilled water maintained at 37 ° ± 0.5°C. The time in seconds for complete disintegration of the oral film with no palable mass remaining in the apparatus was measured and recorded.

In vitro Dissolution Study: The *in-vitro* release of fast dissolving oral film of tramadol hydrochloride was carried out using basket type Electro lab tablet Dissolution tester USPXXIII. Film loaded with drug equivalent to 25 mg of drug was introduced into the 900ml of pH 6.8 phosphate buffer (dissolution medium) maintained at 37 ± 0.5 °C with basket rotating at 50 rpm. Samples are withdrawn and analysed spectrophotometrically using UV-Visible spectrophotometer. The volume

of dissolution medium was adjusted to 900 ml after every withdrawing the sample by replacing 5 ml with same dissolution medium.

Stability Studies: The purpose of stability testing is to provide evidence on how the quality of drug substance or drug product varies with time under the influence of various factors such as temperature, humidity, light and to establish retest period for the drug substance or shelf life for the drug product and recommended storage condition.

The nature of stress testing depends upon the individual drug substance and the type of drug product involved. The stability was conducted on the drug substance packed in a container closure system that is the same as or simulates the packing proposed for storage and distribution. Stability studies for selected formulations were carried out by storing in amber colored bottle tightly plugged with cotton and capped at 40 ± 0.5 °C and $75.0 \pm 5\%$ Rh for 3 months. The formulations were evaluated for physical appearance, drug content

and *in vitro* dispersion time at 1 month interval time.

RESULTS AND DISCUSSION:

Melting Point Determination: The melting point was found to be 171 °C which corresponds to the melting point given in literature.

Ultraviolet Spectroscopy: The values of correlation coefficient for the linear regression equation was found to be 0.999 for phosphate buffer of pH 6.8 indicating a good positive correlation between concentration of tramadol hydrochloride and the corresponding absorbance values.

Compatibility Studies: From FTIR studies it was clear that the drug has not undergone any type of structural change or any chemical reaction with the polymers and other excipients used. Therefore it was concluded that in the present investigation there was no interaction of the drug with the polymers or the excipients used.

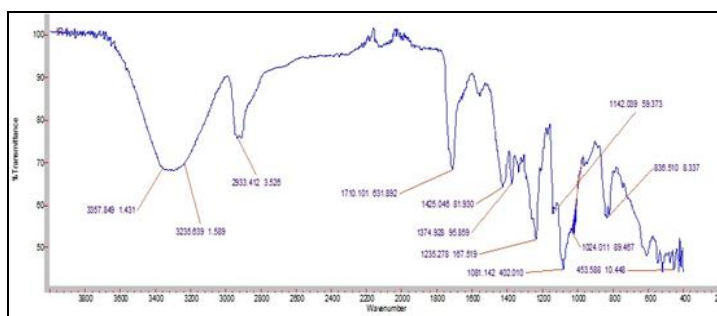


FIG. 1: FTIR SPECTRA OF PURE DRUG

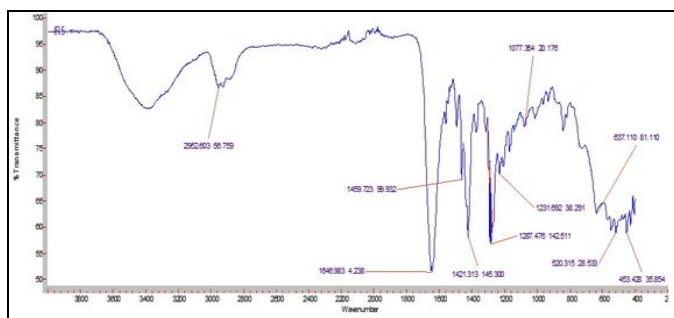


FIG. 2: FTIR SPECTRA OF POLYMER

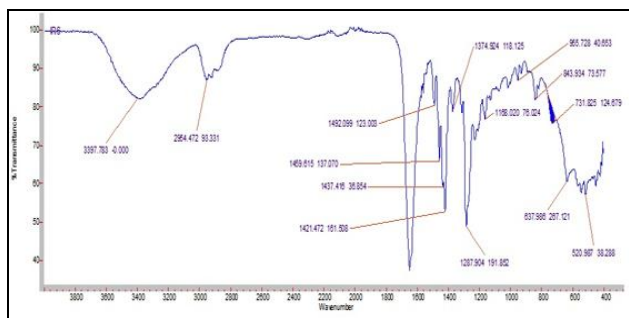


FIG. 3: FTIR SPECTRA OF OPTIMISED FORMULA

Evaluation of Fast Dissolving Films: The tramadol hydrochloride films were evaluated for the following properties:

Thickness of Film: The thickness was almost uniform in all the formulations and values ranges from 0.7 ± 0.057 mm to 1.1 ± 0.100 mm.

The standard deviation values indicated that all the formulations were within the range.

Folding Endurance: The folding endurance of the films was determined by repeatedly folding a small strip of films at the same place till it breaks and values range from 112 - 208.

Moisture Uptake: All the films were free from the moisture uptake and there was no evidence of moisture attack in the prepared films.

Weight Uniformity of Films: The weights of the prepared films were determined using digital balance. The range was within 43 - 57 mg.

TABLE 3: EVALUATION OF FILMS FOR PHYSICAL PARAMETERS

Formulation code	Weight (mg) ± SD, n=3	Moisture uptake	Thickness (mm) ± SD, n=3	Folding endurance ± SD, n=3
F1	56.20 ± 0.57	Nil	0.9 ± 0.15	133 ± 4.50
F2	48.00 ± 1.00	Nil	0.8 ± 0.10	208 ± 2.88
F3	50.32 ± 1.43	Nil	1.1 ± 0.01	144 ± 3.21
F4	47.21 ± 1.00	Nil	0.7 ± 0.05	123 ± 4.72
F5	43.10 ± 0.52	Nil	0.7 ± 0.11	112 ± 2.51
F6	49.27 ± 0.57	Nil	0.8 ± 0.05	162 ± 3.60
F7	57.45 ± 0.22	Nil	1.1 ± 0.10	184 ± 4.04
F8	56.25 ± 0.36	Nil	1.1 ± 0.17	171 ± 3.60
F9	60.29 ± 1.21	Nil	0.9 ± 0.05	133 ± 3.05
F10	47.10 ± 0.57	Nil	0.9 ± 0.20	149 ± 2.08
F11	52.14 ± 0.52	Nil	1.1 ± 0.10	197 ± 2.51
F12	47.66 ± 1.52	Nil	0.8 ± 0.05	123 ± 3.21

Uniformity of Drug Content: The drug content uniformity was performed for all the 12 formulations. The results were within the range and that indicated uniformity of mixing. Values ranges from 88 - 96%.

In vitro Disintegration Study: The *in vitro* disintegration time is the time taken by the film to undergo complete disintegration.

TABLE 4: EVALUATION OF FILMS FOR DRUG CONTENT UNIFORMITY, IN VITRO DISINTEGRATION, SWELLING INDEX

Formulation code	Drug content uniformity (%) ± SD, n = 3	In vitro disintegration (sec) ± SD, n = 3	Swelling index (%) ± SD, n = 3
F1	96.65 ± 0.05	31 ± 1.00	62.22 ± 3.84
F2	90.87 ± 0.01	19 ± 1.42	54.16 ± 3.60
F3	91.27 ± 0.06	42 ± 2.88	65.27 ± 2.40
F4	95.94 ± 0.03	22 ± 2.51	58.33 ± 3.60
F5	93.91 ± 0.04	19 ± 3.60	64.65 ± 2.26
F6	91.27 ± 0.04	38 ± 2.51	63.80 ± 3.92
F7	89.55 ± 0.02	49 ± 2.88	52.08 ± 3.60
F8	90.06 ± 0.02	45 ± 1.05	48.66 ± 3.39
F9	95.63 ± 0.03	19 ± 1.52	56.60 ± 5.92
F10	91.58 ± 0.04	38 ± 2.51	57.77 ± 3.85
F11	88.33 ± 0.02	47 ± 2.64	65.79 ± 4.44
F12	92.90 ± 0.05	22 ± 1.00	60.24 ± 2.23

TABLE 5: IN VITRO DISSOLUTION STUDIES DATA

Time (min)	% released											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
1	51.94	47.3	57	49.1	40	26.7	2.25	12.8	10.8	52.9	30	75.5
3	73	61.7	47	66.3	63	51.4	27	31.8	29.8	24.6	2.41	98
5	86.4	76.6	57	83.3	72.5	101.3	41	45.1	41.1	34.4	28	105.4
10	114	99.7	82	87.4	80	133	68	64.8	60.8	48	44.7	
15	125	122.9	97	79.7	96.6	106	77	85.8	81.8	50	51.9	
30	125	126	103	82.7	91.5	96	82	90.5	84	60.6	60.6	
45	121	122	104	79.7	105	98	85	94.6	90.5	123	119	

In vitro Dissolution Study: Film loaded with drug equivalent to 25 mg of was introduced into 900 ml of pH 6.8 phosphate buffer (dissolution medium) maintained at 37 ± 0.5 °C with basket rotating at 50

rpm. Samples are withdrawn and analyzed spectrophotometrically using UV-Visible spectrophotometer. F12 showed 98% release within 3 min.

Reasons for fluctuations of release depend on the selection of polymer, as sodium alginate is a hydrophilic polymer while HPMC (E5, E6, and E15) are hydrophobic polymers the release mechanism differs. Sodium alginate attains water to dissolve the drug quickly and it gets dispersed, hence sudden increase of drug release was seen.

But in HPMC cases being hydrophobic the matrix formed gets so rigid and drug remains intact within the polymer matrix. Hence film cannot adhere, hydrates, and dissolve quickly to release the medication for intra gastric absorption. Thus release rate retards.

TABLE 6: DRUG RELEASE KINETIC PARAMETERS FOR FORMULATIONS 1-12 OF FILMS

Formulation code	R ²				
	Zero	Higuchi	Peppas	First	Hixson Crowell
F1	0.7777	0.9332	0.9922	0.9559	0.9750
F2	0.8497	0.9707	0.9819	0.9184	0.9750
F3	0.7411	0.8079	0.3700	0.8130	0.7630
F4	0.4806	0.8986	0.9514	0.8485	0.7881
F5	0.7244	0.9183	0.9517	0.8480	0.7925
F6	0.7790	0.9543	0.9512	0.9582	0.9825
F7	0.9299	0.9221	0.9227	0.9944	0.9928
F8	0.9554	0.9843	0.9883	0.9920	0.9800
F9	0.9623	0.9802	0.9834	0.9915	0.9807
F10	0.3359	0.4014	0.0185	0.2187	0.2342
F11	0.6920	0.5289	0.0408	0.5977	0.5798
F12	0.7040	0.9180	0.370	0.936	0.9838

Stability Studies: Stability studies were conducted on the best release formulation F12. No visible changes were observed in the products after storage. The drug content was found to be uniform and within the limits even after storage at (40 °C ± 75% Rh) for 3 months, indicated that there were no significant changes in the drug release even after storage at 40 °C. The drug release characteristics of the product were found to be stable and unaltered.

TABLE 7: STABILITY STUDIES FOR F-12

Parameters	Stability data	
	Initial	3 months (40 °C ± 75% Rh)
Thickness(mm)	0.8±0.05	0.7±0.06
Folding endurance	123±3.21	120±3.20
Drug content	92.90±0.05	92.89±0.05
<i>In vitro</i> disintegration (sec)	22	24
<i>In vitro</i> dissolution (%)	98	98

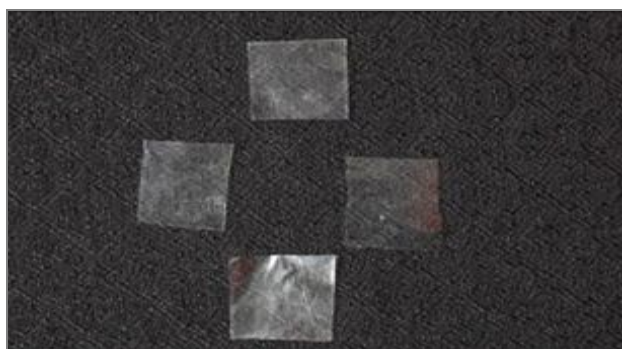


FIG. 4: PHOTOGRAPH OF FAST DISSOLVING ORAL FILM OF TRAMADOL HYDROCHLORIDE

CONCLUSION: Tramadol hydrochloride is used as an analgesic and anti-inflammatory agent. Fast dissolving films of tramadol hydrochloride are useful due to their rapid onset of action. Fast dissolving films are a feasible alternative to the available conventional immediate release dosage forms.

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CONFLICT OF INTEREST: There are no conflict of interest.

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