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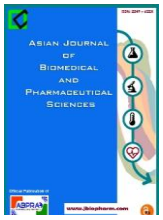

RESEARCH ARTICLE

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Development and Evaluation of Orally Disintegrating Film of Tramadol Hydrochloride

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Abstract
Orally disintegrating films offer advantage of patient compliance over conventional solid dosage forms. Present study aims at formulation and evaluation of orally disintegrating films of Tramadol Hydrochloride which disintegrate within 30 seconds. Polymers like modified pea starch (Lycoat RS 720) and pullulan were evaluated for film forming capacity and were found to form thin, smooth films at 25% w/w and 2% w/w concentration respectively. Two plasticizers, propylene glycol and sorbitol were evaluated. Taste masking of drug was done using sweetener, flavour and flavour extender. Drug content in both films was above 98% and found to release the drug within 15 minutes. Drug loaded films with both the polymers were stable under 25°C/60% RH and 40°C/75% RH conditions.

Keywords: Lycoat RS 720, Orally disintegrating film, pullulan.

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1. 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 disintegrating solid dosage forms when placed upon tongue disintegrate within few seconds to form suspension which can be swallowed easily without water [1]. Orally disintegrating systems like orally disintegrating tablets (ODTs), orally disintegrating films (ODFs) and wafers have carved niche amongst the oral drug delivery systems due to their high patient compliance.

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 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 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 musculosketetal 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.

Like other tablets, patients are sometimes non-compliant with ODTs due to fear of choking. Also ODTs are friable and may break during transport and handling. Orally disintegrating film is a better alternative to ODTs. ODFs when placed on the tip or the floor of the tongue are instantly wet by saliva. As a result, ODFs rapidly hydrate and then disintegrate and/or dissolve to release the medication for local and/or systemic absorption. Hence in chronic and severe pain, ODFs of Tramadol will be choice of patients over ODTs and any other dosage form.

The main objective of present research work is to formulate ODF which will disintegrate within 30 seconds. Polymers like pregelatinised hydroxypropyl pea starch (Lycoat RS 720) 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

2. 1MATERIALS

Tramadol hydrochloride and sucralose were obtained from Rubicon Research Pvt. Ltd., Mumbai, Pullulan from Gangwal Chemicals, Mumbai, Lycoat RS 720 and sorbitol from Roquette Pharma, Mumbai, Soya lecithin from VAV Life Science, Mumbai, Monoammonium glycerrhizinate (Magnasweet) from Mafco Ltd., Mumbai. All other chemicals and reagents were of analytical grade and were purchased from Loba chemicals, Mumbai. Purified water was used for study.

2.2METHODS

3.1. Screening of polymer for ODF:

Polymer films were prepared by solvent casting method according to the formula given in Table 1 and 2. Propylene glycol (PG) 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.

Ingredients	(% w/w composition)						
	LF01	**LF02**	**LF03**	**LF04**	**LF05**	**LF06**	**LF07**
Lycoat RS 720	10	25	25	25	25	25	25
Propylene glycol	2	2	4	4	4	4	4
Polysorbate 80	2	2	2	2	2	2	2
Soya lecithin	-	-	-	-	-	-	-
Crospovidone	-	-	-	2	4	-	-
Polacriline Potassium	-	-	-	-	-	2	4
Purified water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s	q.s.

Ingredients	(% w/w composition)					
	LF08	**LF09**	**LF10**	**LF11**	**LF12**	**LF13**
Lycoat RS 720	25	25	25	25	25	25
Sorbitol	2	2	4	4	4	4
Polysorbate 80	2	-	2	-	0.5	0.1
Soya lecithin	-	2	-	2	0.5	0.8
Purified water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Table 1. Formulation of Lycoat RS 720 films.

Ingredients	(% w/w composition)							
	PF01	PF02	PF03	PF04	PF05	PF06	PF07	PF08
Pullulan	2	2	3	3	2	2	2	2
Propylene glycol	2	2	2	2	1	-	-	-
Polysorbate 80	-	2	-	2	-	-	-	-
Sorbitol	-	-	-	-	-	1	0.5	0.3
Purified water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Table 2. Formulation of Pullulan films.

3.2. Formulation of drug loaded films:

Drug loaded films were also prepared by solvent casting method. 50 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. Since the drug is extremely bitter, sweetener and flavor were used for taste masking. Plasticizer was dissolved into small quantity of purified water. In this plasticized solution, suitable quantity of polymer was added. Polymer was dissolved and the solution was deaerated by sonication. Tramadol hydrochloride along with other excipients was dissolved separately in remaining quantity of water. Both solutions were then mixed under stirring. Homogenous solution was deaerated by sonication. Film was casted on plastic petri plate of diameter of 5.8 cm and dried in oven at 60º C for suitable period of time. Dried films were easily peeled off and then taken up for the further evaluation. Tramadol ODFs were prepared as per formula given in Table 3 and 4.

Ingredients	Concentration (%w/w)
Tramadol hydrochloride	11.6
Lycoat RS 720	25
Sorbitol	4
Soya lecithin	0.8
Polysorbate 80	0.1
Sucralose	1
Magnasweet	0.1
Peppermint powder	0.8
Purified water	q.s. 100 gms

Table 3. Formulation of Tramadol ODF using Lycoat RS 720 (TODF01)

Ingredients	Concentration (%W/W)			
	TODF02	TODF03	TODF04	TODF05
Tramadol hydrochloride	4.6	4.6	4.6	4.6
Pullulan	2	2	2	2
Propylene glycol	1	1	1	-
Corn starch	-	2	1	-
Sorbitol	-	-	-	0.3
Sucralose	1	1	1	1
Peppermint powder	0.8	0.8	0.8	0.8
Magnasweet	0.1	0.1	0.1	0.1
Purified water	q.s.	q.s.	q.s.	q.s.

Table 4. Formulation of Tramadol ODF using Pullulan.

1. EVALUATION OF ODFs

a) Thickness measurement

The thickness of each film was measured at five different locations (centre and four corners) using Vernier caliper micrometer [3]. Data was represented as a mean ± SD of five replicate determinations.

b) Determination of moisture uptake

Films were cut into 2 × 2 cm square strips (4 cm^2). The moisture uptake by the films was determined by exposing them to 75% relative humidity (RH) at room temperature (25 ± 2° C) for one week. The uptake of moisture by the films was measured and calculated as percent increase in weight [4].

c) Tackiness evaluation

Tack is the tenacity with which the film adheres to an accessory that has been pressed into contact with the film [5]. Tackiness evaluation was carried out by gently pressing the film between fingertips and results were noted in qualitative terms as tacky or non-tacky [6].

d) Film softening upon storage

Films were stored in desiccators at room temperature for 48 hours. Films were then evaluated for softening and its integrity.

e) Folding endurance

The folding endurance of the film was determined by repeatedly folding one film at the same place till it breaks. 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 [7].

f) *In vitro* disintegration time

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. Test was conducted in triplicates.

g) Drug content determination

Three samples of 1 cm^2 surface area of film were cut and dissolved in 0.1 N HCl. Tramadol hydrochloride concentration was estimated by UV-Visible spectrophotometer at 271 nm. Content uniformity should be within 85-115% and relative standard deviation should be not more than 6 % [8].

h) *In vitro* dissolution study

The *in vitro* dissolution test was performed using the USPXXX 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 0.1 N Hydrochloric acid. Film size required for dose delivery (2 × 2 cm^2) was used. Five ml aliquot of dissolution media was collected at time intervals of 1, 2, 5, 10 and 15 minutes and replaced with equal volumes of 0.1 N HCl. The collected samples were filtered through 0.45 µm membrane filter and the concentration of the dissolved Tramadol hydrochloride was determined using UV-Visible spectrophotometer at 270 nm. The

results were presented as an average of three such concentrations.

i) Stability study

Films were packed in laminated aluminum foil and were subjected to conditions of 25°C, 60% RH and 40°C, 75% RH for the period of one month. Films were evaluated initially and after one month period for all above mentioned parameters.

5. RESULTS AND DISCUSSION

5.1. Screening of polymer for ODFs:

The present study was undertaken to investigate polymers like Lycoat RS 720 and pullulan for their film forming capacity. Initially investigation was focused on development of polymer films with good peelability from substrate, uniform appearance, non-tackiness, optimum flexibility, *in vitro* disintegration time of less than 30 seconds. Although no requirements for disintegration time have been specified for ODFs, a limit of 30 seconds was decided as a selection criterion for screening studies. For faster disintegration, water soluble polymers like modified starch (Lycoat RS 720) and pullulan were screened at concentration of 10-26% w/w and 2-3% w/w respectively.

As per results of evaluation tests given in Table 5, Lycoat RS 720 at concentration of 25% w/w formed films with good peelability, while at lower concentration of 10% w/w, no film formation was observed. To impart flexibility and improve wetting property of film PG and polysorbate 80 were added. At 2% w/w concentration of PG, film was found to be brittle with low folding endurance. Hence PG concentration to 4% w/w, which resulted in flexible film formation with good folding endurance. For both the trials, polysorbate 80 concentration was fixed i.e. 2% w/w. But Lycoat films were non-disintegrating at both the concentrations of PG. Further trials were taken with superdisintegrants like crospovidone and polacrilin potassium at 2 and 4 % each. 55 seconds was the shortest disintegration time observed at 4% of polacrilin potassium which was not desirable. Films with superdisintegrants were not smooth and uniform in appearance. Also these films picked up moisture and softened when stored packed in aluminum pouch in desiccators for 48 hours at room temperature. This was thought to be due to plasticizer; hence PG was replaced with sorbitol. Superdisintegrants are hygroscopic in nature, which were also contributing to film's instability. Therefore more focus was given to achieve disintegration in minimum time without using superdisintegrants and to reduce the softening due to moisture pick up. Sorbitol was tried at 2% w/w and 4% w/w concentration. It was observed that at 4% w/w concentration of sorbitol film flexibility was maintained without affecting the stability. Soya lecithin helps in wetting and dissolving of film, hence it was incorporated in the films [9]. Lycoat films with 2% w/w soya lecithin were found to be non-tacky unlike the films with 2% w/w polysorbate 80 which were tacky. Folding endurance of film containing polysorbate 80 was more than that of with soya lecithin but latter gave films which disintegrated within 30 seconds. Hence it was decided to combine polysorbate 80 and soya lecithin at 0.5% w/w of each. Though this film was disintegrated in 21 seconds and had high folding endurance, slight tackiness was still there which would have increased during storage. Since this tackiness was due to polysorbate 80, trial was taken by reducing its concentration to 0.1% w/w while soya lecithin was increased to 0.8% w/w to maintain the lower disintegration time. No film softening upon storage was observed. Hence the polymer film of batch no. LF13 was selected for drug loading.

As per results of evaluation tests given in Table 6; pullulan formed good peelable film at 2% w/w and 3% w/w concentration. Disintegration time of 2% w/w pullulan film was lesser than that of 3% w/w pullulan film. Hence lower concentration of pullulan was selected for further trials. Effect of PG and polysorbate 80 on flexibility and tackiness was studied. Films obtained at 2% w/w concentration of PG were flexible with satisfactory folding endurance. But these films picked up moisture upon storage. Hence film was prepared with 1% PG; which was stable on storage. Films with polysorbate 80 at 2% w/w concentration were tacky; therefore it was excluded from formula. Polysorbate 80 did not have significant effect on disintegration of film. Sorbitol was another plasticizer tried for pullulan film at 1, 0.5 and 0.3% w/w levels. Minimum disintegration time was noted for the film with 1% w/w of sorbitol but this film softened upon storage. Also the film was tacky and teared off during peeling. Films with 0.3% w/w sorbitol were non tacky and disintegrated in 15 seconds. Also these films were stable on storage. Hence the polymer film of batch number PF05 and PF08, containing PG and sorbitol respectively were selected for drug loading.

Formulation	LF01	LF02	LF03	LF04	LF05	LF06
Film forming capacity	Bad	Good	Very good	Good	Good	Good
Peelability	Non-peelable	Peelable	Peelable	peelable	Peelable	Peelable
Tackiness	Non-tacky	Non-tacky	Non-tacky	Non-tacky	Non-tacky	Non-tacky
Folding endurance	-	4	29	23	26	25
Disintegration Time	Non-disintegrating			3 minutes 11 seconds	2 mins 29 seconds	1 min 53 seconds
Film Softening on storage	Softening					

Table 5. Evaluation and results of Lycoat RS 720 polymer films

Formulation	LF07	LF08	LF09	LF10	LF11	LF12	LF13
Film forming capacity	Good	Good	Good	Good	Good	Good	Very good
Peelability	Peelable	Brittle during peeling	Non-peelable	Peelable	Peelable	Peelable	Peelable
Tackiness	Non-tacky	Tacky	Non-tacky	Tacky	Non-tacky	Slight tacky	Non-tacky
Folding endurance	29	9	11	28	23	33	31
In vitro Disintegration Time	55 seconds	38 seconds	31 seconds	36 seconds	29 seconds	21 seconds	19 seconds
Film softening upon storage	Softening	No film softening					

Table 5(....continued). Evaluation and results of Lycoat RS 720 polymer films

Formulation	PF01	PF02	PF03	PF04	PF05	PF06	PF07	PF08
Film forming capacity	Very good	Very Good	Very good	Very good	Very good	Very good	Very good	Very good
Peelability	Peelable	Peelable	Peelable	Peelable	Peelable	Peelable	Peelable	Peelable
Tackiness	Non-tacky	Tacky	Non-tacky	Tacky	Non-tacky	Tacky	Non-tacky	Non-tacky
Folding endurance	35-37	30-33	36-37	29-33	39-40	40-42	40-42	36-38
In vitro Disintegration Time (seconds)	15	14	18	17	15	13	15	15
Film softening upon storage	Softening				No film softening	Softening		No film softening

Table 6. Evaluation of pullulan films

5.2. Formulation of drug loaded film:

Results of evaluation tests performed for the characterization of Tramadol hydrochloride ODFs are given in Table 7.

Parameters	TODF01	TODF02	TODF03	TODF04	TODF05
Appearance	Smooth surface and transparent	Smooth surface and transparent	Smooth surface and translucent	Smooth surface and translucent	Smooth surface and transparent
Tack test	Non-tacky	Non-tacky	Non-tacky	Non-tacky	Non-tacky
% Moisture uptake	0.46	1.6	0.82	0.82	0.62
Thickness (mm)	0.34	0.3	0.23	0.34	0.31
Disintegration time (seconds)	26	30	42	29	16
Folding endurance	29	30	4	40	36
Film softening upon storage	No film softening	Softening	No film softening		
% Drug content	101.52 %	99.36%	97.8%	101.4%	100.69

Table 7. Evaluation of Tramadol ODFs

Drug loading into selected 25% w/w Lycoat polymer film yielded films with desired properties. Films of formula TODF01 were non-tacky, smooth and transparent with an average thickness of 0.34 mm. Also disintegration times of these films were within 30 seconds; hence it was observed that drug loading did not affect the initial properties of Lycoat placebo films. *In vitro* dissolution study of TODF01 showed 95% drug release in 10 minutes, given in Fig.1.

Drug loading in formula PF05 which was 2% w/w pullulan polymer film required modification in order to improve film stability. Formula TODF02 resulted in films disintegrating in 30 seconds but picked up moisture upon storage. This was thought to be due to low solid content; hence 2% w/w corn starch was added in the pullulan films. Corn starch made the film translucent and also increased its disintegration time to 42 seconds. But film stability was improved. Further trial was taken at 1% w/w corn starch. Reduction in corn starch concentration causes faster disintegration in 29 seconds. Also no moisture pick up was observed on storage. Drug loading in formula PF08 films with desired properties. Films of formula TODF05 were non-tacky, transparent and were disintegrated in 16 seconds. Unlike films of TODF02 no film softening observed for TODF05. Hence it was confirmed that the film instability for formula TODF02 was due to PG used. While 0.3% w/w sorbitol as a plasticizer, did not create any stability problem even after drug loading hence no additives like corn starch were required. *In vitro* dissolution study of TODF04 and TODF05 showed complete drug release in 10 minutes, given in Fig.1.

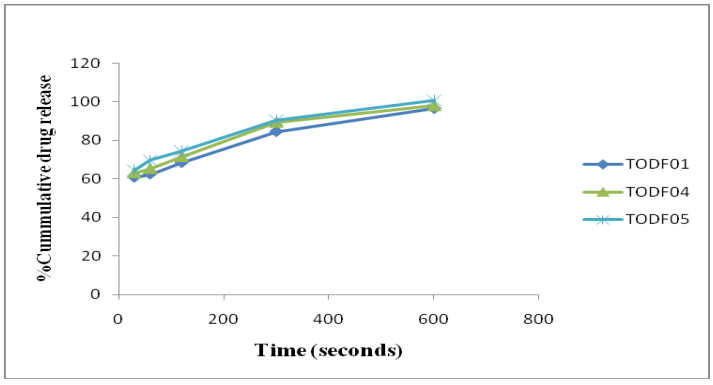

Figure 1: *In vitro* Dissolution profile of drug loaded films

5.3. Stability study:

Drug loaded Lycoat films of formula TODF01 were found to be stable at both the stability conditions. No change was observed in appearance, disintegration time and assay. Drug loaded pullulan films of formula TODF04 showed instability at 40°C, 75% RH. Film softening was observed which was thought to be due to hygroscopic nature of PG. Drug loaded pullulan films of formula TODF05 were found to be stable at both the conditions for one month.

6. CONCLUSION

Film forming capacity of Lycoat RS 720 and pullulan as well as effect of plasticizers on physical properties of film were evaluated. Lycoat at 25% w/w while pullulan at 2% w/w concentration was found to form a film with good peelability. Lycoat RS 720 and pullulan both can form orally disintegrating films of Tramadol Hydrochloride with desirable properties. Use of propylene glycol in Lycoat and pullulan film affected the drug loaded film stability. Sorbitol was the suitable

plasticizer for Lycoat and pullulan film at 4 and 0.3% w/w concentrations respectively. Use of soya lecithin reduced the film disintegration time in case of Lycoat film. Pullulan film had faster disintegration without use of any wetting or solubilizing agent.

7. ACKNOWLEDGMENT

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