

Original Research Article

Development of Oral Fast-Disintegrating Levothyroxine Films for Management of Hypothyroidism in Pediatrics

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Abstract

Purpose: To develop fast disintegrating films of levothyroxine (LVX) using hydrophilic hydroxypropyl methylcellulose (HPMC), croscarmellose sodium (CCS) as superdisintegrant, and propylene glycol (PG) as a plasticizer.

Methods: Fast-disintegrating films were formulated by solvent casting evaporation method using 3-factor, 2-level full factorial design. The films were evaluated for disintegration time, in vitro drug release, physical appearance, thickness, weight variation, folding endurance, drug content uniformity, The effect of concentration of dependent variables (HPMC, CCS and PG) on disintegration time and in vitro drug release was studied.

Results: Suitable fast-disintegrating films were obtained using HPMC, CCS and PG. The minimum disintegration time (DT) was 15 s and maximum drug release (DR) in 1 h was 97.56 %. All independent variables selected for the study were statistically significant ($p < 0.5$). Increase in the concentrations of independent variables increased DR and DT.

Conclusion: The findings of this study indicate that the developed fast-disintegrating film is suitable for levothyroxine in the management of hypothyroidism in pediatrics.

Keywords: Hypothyroidism, Superdisintegrant, Fast-disintegrating, Levothyroxine, Oral films, Hydroxypropyl methylcellulose, Croscarmellose sodium, Propylene glycol

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INTRODUCTION

Hypothyroidism, often referred to as underactive thyroid, low thyroid and sometimes, hypothyreosis, is a common endocrine disorder in which the thyroid gland does not produce enough thyroid hormone [1,2]. It is associated with tiredness, poor ability to tolerate cold, and weight gain. In children, hypothyroidism leads to delay in growth and intellectual development, known as cretinism in severe cases [3]. The age of symptom onset is unpredictable in a child who has thyroid dysgenesis with a hypoplastic and or ectopic thyroid gland because initial increases in Thyroid stimulating hormone (TSH) may be able

to initially overcome the relative insufficiency of the thyroid gland. Newborn children with hypothyroidism may have normal birth weight and height (although the head may be larger than expected and the posterior fontanelle may be open). Some may have drowsiness, decreased muscle tone, a hoarse-sounding cry, feeding difficulties, constipation, an enlarged tongue, umbilical hernia, dry skin, decreased body temperature and jaundice [4,5].

Levothyroxine sodium (LVX) is used for the treatment or prevention of various types of deficiency such as hypothyroidism, cretinism, non-toxic goitre, myxoedema and coma in

newborn, infants and children [6]. LVX is also effective in the suppression of pituitary thyroid stimulating hormone (TSH) secretion in the treatment or prevention of various types of euthyroid goiters. LVX tablets are available in the market for the treatment of hypothyroidism for pediatrics. [7]. One of the greatest challenges in pediatric pharmacology has been optimization of oral drug delivery. In a recent study, 54 % of children between the ages of 6 and 11 years told study investigators that they were unable to easily swallow a tablet [8,9].

Oral fast-disintegrating film containing active drug molecule is a delivery technology for the oral delivery of drugs as an alternative to conventional dosage forms such as tablets, capsules, syrups and other formulations, for pediatric and geriatric use. Oral fast disintegrating films are easy to administer and provide better patient compliance in the elderly, pediatric, mentally retarded, nauseated and uncooperative patients [10]. Thus, the aim of the present study was to develop oral fast-disintegrating films of LVX for the management of hypothyroidism in pediatrics for improved patient compliance.

EXPERIMENTAL

Materials

Levothyroxine (LVX) was purchased from Baoji Guokang Bio-Technology Co., Ltd. (Baoji, Shaanxi, China), hydroxypropyl methylcellulose (HPMC) and croscarmellose sodium (CCS) was purchased from Sigma Aldrich, USA. Propylene glycol and sorbitol were purchased from Shanghai Chemical Co. (Shanghai, China).

Preparation of fast disintegrating films

Fast-disintegrating film of LVX was prepared by solvent-casting evaporation method [11]. The composition of the formulation is presented in Table 2. The required quantity of polymer (HPMC) and plasticizer (propylene glycol) was dissolved in double distilled water. This polymeric dispersion was stirred for 1 h using magnetic stirrer at 500 rpm and kept aside to remove all the air bubbles entrapped. In another beaker the aqueous solution was prepared by dissolving specified quantities of LVX, CCS and sorbitol in specific proportion in the mixture of distilled water and alcohol. Polymeric dispersion was added to solution containing LVX and stirred for 1 h. After removal of air bubbles, the polymeric solution containing drug was casted into glass petridish of specified dimension (30 cm²) and dried in the

vacuum oven at 28 °C for 24 h. The film was carefully removed from the Petri dish, observed for any imperfections and cut into circular pieces (5 cm²).

Table 1: Variable and three levels

Variable	Low level (-1)	High level (+1)
Independent		
A= HPMC Conc.	30	40
B= CCS Conc.	2	4
C= PG Conc.	10	15
Dependent		
Y1= DT		
Y2=%DR		

2³ factorial design for formulation of films

Statistical analysis of the experimental work was carried out using Design Expert 6.0.8 portable software. A 3-factor, 2-level full factorial design was used to derive a second order polynomial equation. Concentration of HPMC (A), CCS (B) and Propylene glycol (C) were selected as independent variables while disintegration time (Y1) and in vitro drug release (Y2) were selected as dependent variables. Variables and three levels are presented in Table 1.

Table 2: Formulation of LVX fast disintegrating films using 2³ Factorial Design

Batch	Factor			Response	
	A	B	C	Y1	Y2
F1	+1	+1	+1	15	97.56
F2	+1	-1	+1	52	85.29
F3	+1	-1	-1	45	80.78
F4	-1	+1	+1	25	88.32
F5	-1	+1	-1	18	92.3
F6	+1	+1	-1	20	90.11
F7	-1	-1	+1	55	82.35
F8	-1	-1	-1	60	78.25

Physical evaluation of films

Smoothness, color, clarity, transparency of oral films was examined visually. Thickness of film formulations were evaluated by using micrometer screw gauge. The thickness of 5 film pieces was taken and the mean was taken. The surface pH of the film was determined by placing the film in petridish, slightly wet with the help of distilled water. The pH was noted by bringing the surface of the film in contact with pH meter electrode for one minute. Folding endurance test was performed by repeatedly folding the film at the same place until it broke. The number of times the film could be folded at the same place without breaking or cracking gave the value of folding endurance [12].

Content uniformity test

Each film was soaked and dissolved in 20 ml of dichloromethane and resulting solution was filtered to remove undissolved residue. Aliquots were prepared and measured for drug content at 297 nm using UV spectrophotometer (Schimadzu 1700) [13].

In vitro disintegration time (DT) test

In vitro DT of each film was determined in pH 6.8 phosphate buffer. Approximately 25 ml of 6.8 phosphate buffer was placed in a Petri dish. The film (1 cm²) to be evaluated for DT was placed in this petri plate and time taken by each film to complete disintegrate was noted and considered as DT [13].

Ex vivo permeation studies

Ex-vivo permeation studies were carried out through porcine oral mucosa using specially designed glass diffusion cell. All animal procedures were conducted in accordance with all appropriate regulatory standards according to the protocol approved by the Institutional Animal Care and Use Committee of the Xinxiang Medical University (approval no. Xing/col/FA2145). The animal studies were performed as per the international CPCSEA guidelines. Porcine oral mucosa was soaked previously for 24 h in pH 6.8 phosphate buffer [10,13]. This oral mucosa was stretched around one end of the diffusion cell. The working surface area of the membrane was 3.5 cm². Donor compartment (tube) was adjusted into a glass beaker containing pH 6.8 phosphate buffer (receptor compartment) in such a way that, the oral mucosa just touched the receptor medium. 1 cm² weighed buccal film was placed on the oral mucosa. The receptor medium was maintained at 37 ± 0.5 °C and stirred at 50 rpm. 5 ml aliquots of samples were withdrawn from the receptor medium at predetermined time intervals and replaced with equal volume of fresh buffer to maintain the sink condition. Samples were

analysed with UV-Spectrophotometer at 297 nm and drug release was calculated.

Data analysis

Statistical analysis of the experimental work was carried out using Design Expert 6.0.8 portable software. A 3-factor, 2-level full factorial design was used to derive a second order polynomial equation. The contour plots were constructed to identify the effects of independent variables on dependent variables.

RESULTS

Physical characteristics of films

LVX fast disintegrating films were prepared by solvent casting evaporation technique were transparent, smooth, soft, and colorless in nature. Drug content uniformity of was in the range of 97.59 to 99.58 % while the while thickness of the film was in the range of 0.17 to 0.30 mm. Folding endurance of the film ranged from 160 to 200, and pH of the film was 6.63 to 7.13. All the physical parameters are summarized in Table 3.

DISCUSSION

Patient compliance, convenience of administration of the dosage form and safety are the major factors considered during the development of the dosage form for pediatric patients suffered from disorders of the endocrine system like hypothyroidism, goiter etc [14]. Commercially available dosage forms for pediatrics like tablets, capsules, oral liquid medications have lot of disadvantages e.g. patient compliance, inability to swallow a dosage form [14]. So in order to avoid such drawbacks fast disintegrating films offer great potential for rapid and convenient drug delivery technology for the pediatric patients.

Table 3: Physical characteristics of films

Batch	Drug content (%)	Folding endurance	Thickness (mm)	pH	Film nature
F1	98.90	200	0.17	6.70	Transparent
F2	99.20	175	0.20	7.13	Smooth
F3	98.50	185	0.22	6.90	Smooth
F4	99.56	145	0.25	6.87	Soft
F5	97.59	220	0.24	6.73	Soft
F6	99.58	160	0.30	6.90	Smooth
F7	98.54	180	0.23	6.63	Transparent
F8	97.80	165	0.21	6.65	Transparent

Such fast disintegrating films are more acceptable to patients with hypothyroidism, goiter, dysphagia in pediatric patients. These films are mainly consisting of hydrophilic polymer, superdisintegrants, plasticizers, sweeteners etc which gets dissolved in mouth within seconds. In this experiment the minimum DT of 15 seconds was successfully achieved by using CCS as a superdisintegrant. These films are to be placed on the tongue for oral absorption, under the tongue for sublingual absorption. Such route bypass gut absorption and delivery into the hepatic portal system, thus avoiding the first pass metabolism and increasing the bioavailability[20]. The first FDA approved oral disintegrating film is ondendetron (Zuplenz®) which was approved on 2010. Also several films of rizatriptan, rotavirus vaccine and levocetizine have been under development. These developments and FDA approval clearly indicates the importance of these films in pediatrics and other type of patients who have problem of swallowing and patient compliance[15].

In vitro disintegration time (DT) was determined in 6.8 pH phosphate buffer. Generally the pH of saliva ranges from pH 6.2 – 7.4. DT was 15 to 60 s as shown in Table 4.

From the results presented in Table 4 it clearly indicated that the formulated films had fast disintegrating nature at saliva pH. The polynomial equation obtained for DT (Y1) is given in Eq 1.

$$Y1 = + 36.25 - 3.25A - 16.75B + 0.50C + 0.000BC \dots (1)$$

where Y1 is the DT, A is HPMC concentration, B is CCS concentration and C is propylene glycol concentration.

Table 4: DT and % DR at t = 1 h

Batch	DT (s)	DR (%)
F1	15	97.56
F2	52	85.29
F3	45	80.78
F4	25	88.32
F5	18	92.30
F6	20	90.11
F7	55	82.35
F8	60	78.25

The model F- value 0.0160 indicates the model is significant ($p < 0.05$). A positive value in above equation represents the synergistic effect of the independent variable and a negative value represents the antagonistic effect [16]. The suggested model for the Y1 was found to be 2FI as shown in Table 5.

The value of correlation coefficient (R^2) for the response Y1 was 0.9650 which indicates good fit for the 2 FI model. The p -value for the Y1 model was 0.0160 which clearly indicates the model is statistically significant, viz, the three independent variables selected for all the factors: A ($p = 0.0045$), B ($p = 0.0030$), C ($p = 0.0035$). The data are shown in Table 6.

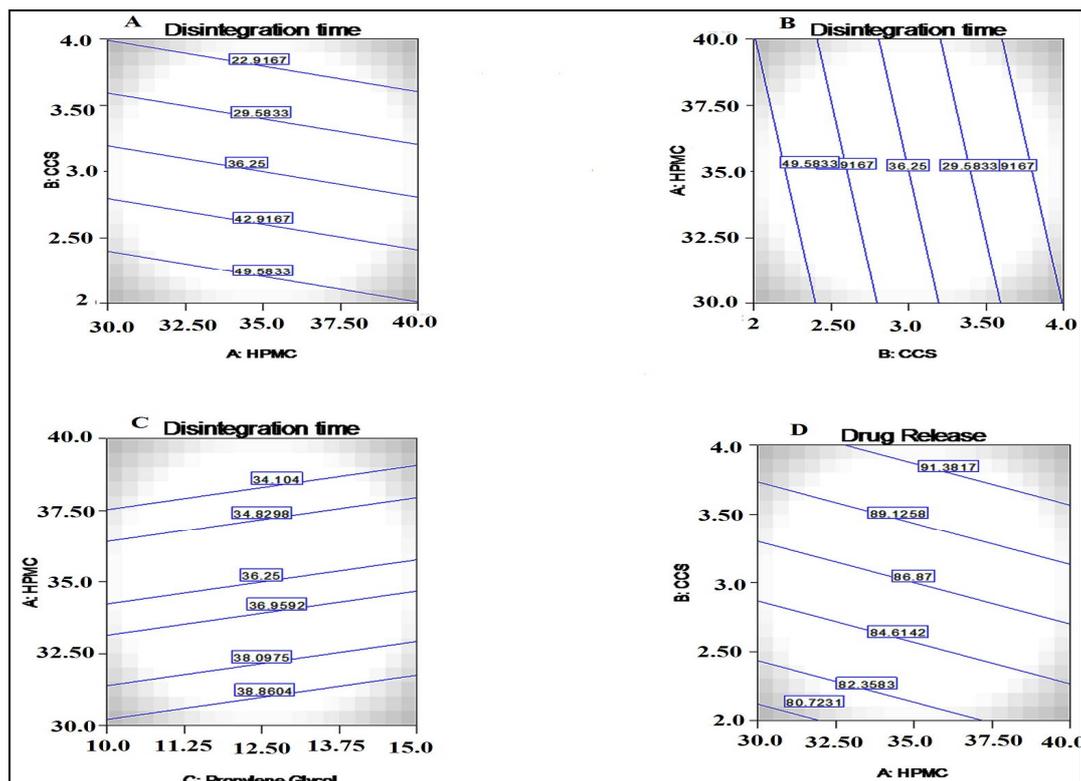
The polymer used for the preparation of film had good film forming property with non-toxic, non-irritant, good wetting properties [10]. This polymer played important role in imparting necessary mechanical properties to the film. It also influenced the DT of the film. As can be seen from contour plot Figure 1(A) as the concentration of HPMC increases from 30 to 40 % the DT of the patches was found to be increased. Increase in the concentration of HPMC had a negative effect on DT of films.

Table 5: Summary of results of regression analysis for responses Y1 and Y2

Model	R^2	Adjusted R^2	Predicted R^2	Std. Dev	Press	Remarks
Response Y1						
Linear	0.8260	0.8035	0.6514	7.36	510.20
2FI	0.9650	0.9184	0.7512	5.31	600.89	suggested
Quadratic	0.9265	0.9072	0.7825	0.45	550.30
Cubic	0.9120	0.8966	0.5912	0.49	462.20
Response Y2						
Linear	0.6599	0.6090	0.3563	3.75	120.73
2FI	0.9353	0.8491	0.5402	2.50	133.65	suggested
Quadratic	0.9020	0.8871	0.8598	4.90	112.30
Cubic	0.9114	0.9025	0.8790	6.50	125.36
Regression equations of the fitted models						
Y1 = +36.25-3.25A-16.75B+0.50C+0.000BC						
Y2 = +86.87+1.57A+5.20B+1.51C+1.48AC						

Table 6: ANOVA of models for Y1 and Y2

Source	DF	Sum of squares	Mean square	F-value	P-value
Model for Y1	4	2331	582.75	20.69	0.0160
A	1	84.50	84.50	3.00	0.0045
B	1	2244.50	2244.50	79.69	0.0030
C	1	2.00	2.00	0.071	0.0035
BC	1	0.000	0.000	0.000	1.000
Model for Y2	4	271.89	67.97	10.85	0.0395
A	1	19.59	19.59	3.13	0.0351
B	1	216.53	216.53	34.56	0.0098
C	1	18.24	18.24	2.91	0.02865
AC	1	17.52	17.52	2.80	0.1930

**Figure 1:** (A):Effect of HPMC on DT of film; (B): Effect of CCS on DT of film; (C): Effect of PG on DT; (D): Effect of HPMC on DR from the films

From above polynomial equation it was also clear that the HPMC concentration (A) has negative effect on DT as coefficient of A is -3.25. The possible reason for such increase in DT was the formation of more dense polymeric dispersion that led to resist in disintegration of the formed film [17].

CCS was used as a superdisintegrant in films to minimize the DT of the oral films containing the LVX. From the contour plot in Figure 1(B), it is clear that as the concentration of CCS increased the DT get decreased. This effect was statistically significant B ($p = 0.0030$). The minimum DT was 15 s at concentration of 4 % CCS. CCS has been already utilized in tablets, capsules and films to adjust the DT of the

formulation. CCS is having great swelling and minimum gelling capacity at low concentration ranging from 2.0 to 6.0 %. Above 8.0 %, it shows higher gelling property with increased viscosity that result into increase in DT. So in this study the concentration was maintained at 2.0 and 4.0 %. CCS is a cross linked polymer of carboxymethyl cellulose sodium. Cross linking makes it insoluble, hydrophilic, highly absorbent material, resulting in excellent swelling properties and its unique fibrous nature gives it excellent water wicking capabilities [18].

Propylene glycol was used as a plasticizer to impart strength to the oral film. Also it was responsible for increasing the flexibility, preventing brittleness or breakage of the film. In

this film development the PG was used in two levels (10 and 15 %). The PG had also negative effect on the DT. As the concentration of PG was increased from low level to high level, the DT was found to be increased as in Figure 1(C). But increasing concentration of PG had improved the strength of the film making it more acceptable for oral use. Plasticizer act by inserting themselves between the polymer strands and break the polymer-polymer interactions and increases the molecular mobility of the polymer strands [19]. Greater physical strength at higher levels of PG led to higher impart resistance to break the film, resulting in increased DT.

Drug release study was carried out at saliva pH (6.8) to simulate the condition. The drug release was found to be in the range of 78.25 to 97.56 % as shown in Table 4. The polynomial equation for DR as given in Eq 2.

$$Y_2 = +86.87+1.57A+5.20B+1.51C+1.48AC.... (2)$$

The model *F*-value 0.0395 indicates the model is significant ($p < 0.05$). The suggested model for the Y_2 was found to be 2FI as shown in Table 5. The value of correlation coefficient (R^2) for the response Y_2 was 0.9353 which indicates the good fit for the 2 FI model. The p -value for the Y_2 model was found to be 0.0395 which clearly indicates the model is statistically significant. Also among the three independent variables selected all factors A ($p = 0.0351$), B ($p=0.0098$), C ($p = 0.02865$). Data shown in Table 6. Diagnostics case statistics for various response

variables are shown in Table 7. Comparative DR profile is given in Figure 2.

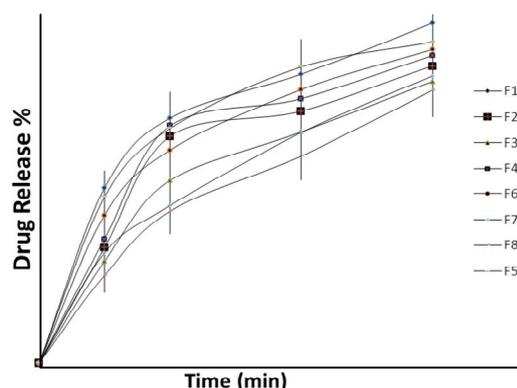


Figure 2: Comparative drug release profile of the films in 6.8 pH phosphate buffer

From the contour plot Figure 1 (D), drug release decreased as the amount of polymer increased from 30 to 40 %. As HPMC form a matrix at physiological pH, it retarded the release of the drug from the film. Hence at higher concentration of the polymer, drug release was lower compared to the lower level of polymer concentration. HPMC is the hydrophilic polymer which absorbs the water and forms the gel this gel is responsible for the retardation of the drug from the film system. Hydrophilic polymers create the pore and the channels on the film surface that led to release of the drug from the film [20]. The effect of HPMC on DR was found to be statistically significant. The CCS has also a significant effect on the DR. The effect is shown in Figure 3(A). As discussed above it also has the swelling property.

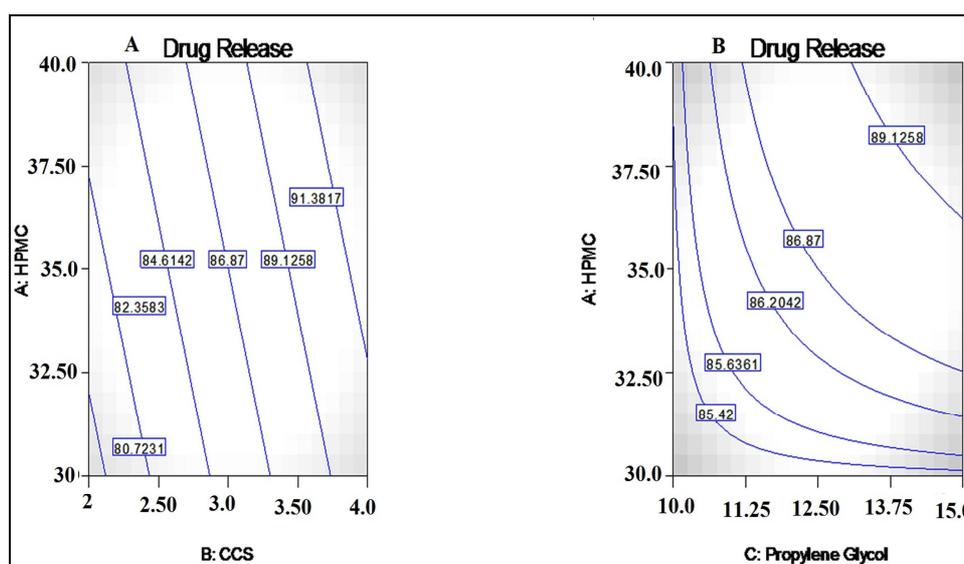


Figure 3: (A) = Effect of CCS on DR from the films; (B) = Effect of PG on DR from the films

Due to swelling of the film it favored the release from the film. Due to disintegrant property of CCS, it helped to break the film at saliva pH and that resulted in to the fast release of the LVX from the film. CCS has positive effect on DR as that seen in DT. DR from the film system was also affected by concentration of plasticizer and it had a direct relationship when the concentration of the plasticizer was increased as shown in Figure 3 (B). A positive coefficient in above equation clearly indicates the favourable effect on the DR. LVX oral fast disintegrating films has also been developed with the intention to improve the patient compliance in pediatrics who are suffering from the endocrine disorder hypothyroidism and goiter. These films had great pharmaceutical acceptance in terms of the physical appearance, strength, pH, folding endurance, uniform drug content within films. All selected independent variables had great influence on DT and DR. HPMC being hydrophilic polymer played great role in the development of the LVX films. HPMC imparted good strength to the films and controlled the release from the films. Also CCS was the key excipient in the films to maintain the DT at saliva pH. Its mechanism is already discussed in result part. The effect of CCS was found to be statistically significant in case of both independent factors. The same effect was observed in case of the PG. Definitely these oral fast disintegrating films could be novel technology for the pediatric patients for the management of the hypothyroidism.

CONCLUSION

Oral fast disintegrating LVX films can be successfully prepared using the HPMC, CCS and PG. Such an oral fast disintegrating film is a potentially suitable delivery system for pediatric patients who have swallowing problem of other solid dosage forms, and can thus be used in the management of hypothyroidism in these patients.

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