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FORMULATION, DEVELOPMENT AND EVALUATION OF FAST DISSOLVING ORAL FILM OF LEVOSULPIRIDE

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ABSTRACT

Fast dissolving oral film (FDOF) is used as a novel approach, as it dissolves rapidly in mouth and directly reaches to the systemic circulation. Oral film technology fulfills all the requirements of potential solid dosage form. The present study was aimed to formulate and evaluate fast dissolving oral films of Levosulpiride using Hydroxy Propyl Methyl Cellulose (HPMC), Sodium Starch Glycolate, Crospovidone, Croscarmellose Sodium, Mannitol and Citric Acid. The suitable plasticizer and its concentration were selected on the basis of flexibility, tensile strength and stickiness of the film. The films are prepared by solvent casting method and characterized by UV, FTIR studies. The films were evaluated for disintegration time, folding endurance, thickness, percentage of moisture content, drug content and *in-vitro* dissolution studies. The F8 formulation has given 99.85% drug release within 10 minutes.

Keywords: Fast dissolving oral films, HPMC, solvent casting, plasticizer, Levosulpiride.

INTRODUCTION

Fast dissolving oral films (FDOFs) or Oral wafers or Oral strips (OS) or sublingual strips or oral thin films (OTF) are the most advanced form of oral solid dosage form due to more flexibility and comfort. It improves the efficacy of APIs by dissolving within minute in oral cavity after the contact with saliva without chewing and no need of water for administration[1-3]. It gives quick absorption and instant bioavailability of drugs due to high blood flow and permeability of oral mucosa is 4-1000 times greater than that of skin. The Levosulpiride is an analytical antipsychotic agent, gastroprokinetic agent and schizophrenia also used that blocks the presynaptic dopaminergic D2 recepters. The present study was deign to formulate fast dissolving oral film of Levosulpiride[4].

MATERIALS AND METHOD

Material

Levosulpiride was procured as gift sample from pharmaceutical company, Hydroxypropyl methylcellulose, Sodium Starch Glycolate, Crospovidone, Croscarmellose Sodium, Mannitol and Citric acid were procured commercially. All the reagents and solvents were used analytical grade.

Formulation of fast dissolving oral film

Levosulpiride containing fast dissolving films were fabricated by the solvent casting method[4].HPMC is known for its good film forming properties and has excellent acceptability. Hence, various grades of HPMC namely HPMC K4 and HPMC K15 were evaluated as film formers. For the fabrication of films, glycerin was used as a humectant. PEG 400 is also reported as lubricant and solubilizer. Therefore, PEG 400 along with glycerol was also used for fabrication of films. Apart from these film formers, SSG (Sodium starch glycolate), CP (Crospovidone) and CCS (Croscarmellose sodium) alone or in combination with each other along with other excipients were tried. Citric acid for saliva stimulating agent and mannitol as sweeteners used to fabricate the films. The composition of various formulations is given in Table 1. The polymer was soaked in water for 30 min or heated in water bath to 80° to get a clear solution. Then a plasticizer was added to it and mixed so as to get homogeneous solution. This solution was then casted onto glass moulds (15*5cm) and was dried in hot air oven at 45° for 24 h [5].

Table 1: Selection and optimization of film forming agents

Name of ingredients (mg) (mg for 12 strips)	F1	F2	F3	F4	F5	F6	F7	F8	F8
Levosulpiride	300	300	300	300	300	300	300	300	300
HPMC K4	50	75	100				25	37.5	50
HPMC K15				50	75	100	25	37.5	50
PEG-400	50	50	50	50	50	50	50	50	50
SSG	50	75		-	-	-	25		37.5
CCS	-	-	50	75	-	-	25	37.5	
CP	-	-	-	-	-	-	-	37.5	37.5
Mannitol	20	20	20	20	20	20	20	20	20
Citric acid	20	20	20	20	20	20	20	20	20
DM water qs to (ml)	20	20	20	20	20	20	20	20	20

Dose calculations

- Width of the plate = 5cm
- Length of the plate = 12cm
- No. of 2.5 x 2.5 cm^2 films present whole plate = 12
- Each film contains 25 mg of drug.
- 12 no. of films contains mg of drug = 25×12 = 300mg
- The amount of Levosulpiride added in each plate was approximately equal to 300mg.

Evaluation of prepare fast dissolving oral films:

Thickness

The thickness of patches was measured at three different places using a vernier caliper.

Weight uniformity

For each formulation, three randomly selected patches were used. For weight variation test, 10 films from each batch were weighed individually by digital electronic balance and the average weight was calculated [6].

Folding Endurance

This was determined by repeatedly folding one film at the same place until it broke. The number of times the film could be folded at the same place without breaking cracking gave the value of folding endurance.

Percentage of Moisture Content

The films were weighed individually and kept in desiccators containing activated silica at room temperature for 24 hrs. Individual films were weighed repeatedly until they showed a constant weight. The percentage of moisture content was calculated as the difference between initial and final weight with respect to final weight[7].

Drug Content Analysis

The film taken into a 10 ml volumetric flask and dissolved in methanol and volume was made up with 10 ml methanol. Subsequent dilutions were made and reacted by UV spectrophotometer at 294 nm [9].

Disintegrating time

Disintegration time was measured by placing the film strip in a Petri dish 6 cm in diameter containing 6 ml of phosphate buffer of pH 6.8. Time required for complete disintegration of the film was noted. All the measurements were done in triplicate and average values was reported [9].

***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 50 rpm in 900 ml

phosphate buffer (pH 6.8). Film size required for dose delivery (2.5×2.5 cm^2) was used. 5 ml aliquot of dissolution media was collected at time intervals of 1, 2, 4, 6, 8, and 10 minutes and replaced with equal volumes of phosphate buffer (pH 6.8). The collected samples were filtered through 0.45 μm membrane filter and the concentration of the dissolved drug was determined using UV-Visible spectrophotometer at 294nm [10].

Stability studies

Stability studies were carried out with optimized formulation F8which was stored for a period of one, two and three months at 40±2ºC temperature and 75±5% relative humidity for a period 3 months. The % Assay of formulation was determined by U.V. spectrophotometer using calibration curve method. The % assay of film was found to slightly decrease at higher temperature.

RESULTS AND DISCUSSION

The average weight of the films was measured in triplicate for each film and found in the range from 40±4– 48±2mg. Formulations F1-F9 folding endurance was in the range of 125±5-185±3. The observed folding endurance data of the films developed with various viscosities and concentrations of film formers indicated that the increase in viscosities and concentrations of the film lead to increase in the folding endurance of the films. The formulations F1-F9 developed with different concentrations of SSG, CCS and CP, disintegration time were found in the range of 12±3 sec to 45±3sec. The formulations F8 prepared with CCS and CP having different concentrations were ranging from 12±3 sec. The data of disintegration time indicates that increasing the concentrations of polymer along with different viscosities tends to increase the disintegration time Table 2.

The formulated OFDFs were evaluated and the % moisture content was calculated. Reduced % moisture content was observed with increase in polymer concentration varying from 1.45±0.65% to 4.52±0.45% w/w for Levosulpiride films Table 3.

The Content uniformity was worked out on individual films of 10 samples. A film of size 2.5*2.5cm^2 was cut and kept in 10ml of volumetric flask containing solvent. This was then shaken in a mechanical shaker till it was dissolved to get a homogeneous solution and then filtered. The drug was determined spectroscopically after appropriate dilution and measured. For F1–F9 formulations developed with HPMC K4 and K15 and superdisintegrants (SSG, CCS and CP) with different concentrations the drug content was found in the range of 98.12±0.45 -99.85±0.18% Table 3.

Even though all the formulations drug content within the specification range. Cumulative % drug release was calculated on the basis of drug content of Levosulpiride present in the respective film. Cumulative % drug release was calculated on the basis of drug content of Levosulpiride present in the respective film. The results obtained in the in vitro drug release for the formulations were tabulated in table. The formulations F1, F2, F3, F4, F5, & F6 show drug release up to 92.12-96.65% at the end of 10min. Rapid drug dissolutions were observed in F8, which release 99.85% respectively. The optimized formulation (F8) shows highest percent of drug release at the end of 10 min. The initial release of the optimized formulation was more (33.32%) when compared with innovator product, therefore the onset of action was very quick compare with the innovator product. In vitro release rate study of optimized formulation Vs conventional marketed tablet has shown that F8 release was found to be faster and complete within 8 min. In vitro release of marketed product was found to be 52.12 in 10 min Table 4.

Table 2: Evaluation of prepared film for General Appearance, Thickness and weight

Formulation code	General Appearance	Thickness* (µm)	Weight* (mg)
F1	Transparent	32±3	40±4
F2	Transparent	34±2	46±2
F3	Transparent	36±3	46±4
F4	Transparent	30±4	40±2
F5	Transparent	34±2	42±3
F6	Transparent	36±5	43±4
F7	Transparent	32±2	42±2
F8	Transparent	36±3	46±3
F9	Transparent	31±4	48±2

***Average of three determination (n=3±SD)**

Table 3: Result of Folding Endurance, Disintegrating time, Tensile strength, Percentage Moisture Content and % Assay

Formulation code	Folding endurance (Times)	Disintegrating time (Sec.)	Tensile strength in kg/cm^2	Percentage of Moisture Content	% Assay
F1	125±5	45±3	0.69±0.05	4.52±0.45	98.45±0.32
F2	136±6	40±4	0.65±0.06	4.32±0.35	98.12±0.45
F3	142±5	42±5	0.72±0.07	3.85±0.25	97.85±0.32
F4	135±4	38±6	0.75±0.05	3.65±0.14	98.98±0.45
F5	132±5	35±5	0.65±0.03	3.12±0.23	98.45±0.65
F6	145±6	30±4	0.73±0.04	2.15±0.15	97.78±0.74
F7	138±2	26±2	0.61±0.06	1.45±0.65	98.45±0.12
F8	185±3	12±3	0.65±0.05	2.05±0.54	99.85±0.18
F9	142±4	19±2	0.58±0.04	1.85±0.41	98.47±0.32

***Average of three determinations (n=3±SD)**

Table 4: *In-vitro* drug release study of Formulation F1-F9

Time (Min.)	Cumulative % Drug release									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	Marketed Formulation
1	25.65	22.32	20.14	24.65	25.45	28.89	32.25	33.32	32.25	12.25
2	45.58	40.32	42.32	42.23	45.56	42.12	55.65	48.85	45.56	25.45
4	54.45	50.36	56.65	52.12	50.23	58.85	68.85	69.98	65.58	36.65
6	69.98	62.12	70.23	65.45	67.78	69.98	86.65	73.32	70.23	45.58
8	88.12	85.65	91.14	81.12	85.45	86.65	92.32	95.45	85.65	48.02
10	92.12	93.32	94.65	90.36	93.32	96.65	96.65	99.85	96.65	52.12

Table 5: Results of *in-vitro* release Kinetics of optimized formulation F8

Time (min.)	Square Root of Time(h)$^{1/2}$	Log Time	Cumulative*% Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
1	1	0	33.32	1.523	66.68	1.824
2	1.414	0.301	48.85	1.689	51.15	1.709
4	2	0.602	69.98	1.845	30.02	1.477
6	2.449	0.778	73.32	1.865	26.68	1.426
8	2.828	0.903	95.45	1.980	4.55	0.658
10	3.162	1	99.85	1.999	0.15	-0.824

Table 6: Comparative study of regression coefficient for selection of optimized batch

	Zero order	First order	Higuchi	Peppas model
r^2	0.947	0.803	0.975	0.983

Table 7: Characterization of stability study of Optimized formulation

Characteristic	Time (Month)			
	Initial	1 Month	2 Month	3 Month
% Assay*	99.45±0.41	99.12	98.85	98.50

***Average of three determinations (n=3)**

CONCLUSION

From the latest research it can be inferred that fast-dissolving oral films of drug release are preferable. The films prepared by HPMC K4 and K15 and CCS and CP had shown strong mechanical power, release of narcotics, period for disintegration and analysis of dissolution. F8 formulation is considered the better with less disintegrating time and release in 10 min according to the results obtained. Percent drug release and disintegration time was taken as responses for study which were found within the accepted ranges. Levosulpiride administered in the form of fast dissolving films will be potential novel drug dosage form for pediatric, geriatric and also for general population by providing faster release and better patient compliance.

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