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FORMULATION AND EVALUATION OF MOUTH DISSOLVING FILMS OF ZOLPIDEM TARTRATE BY EXPLORATION OF POLYMERS COMBINATION

M.K. Patidar, F.A. Karjikar, F.A. Patel, S.S. Rathi, S.B. Thokal, C.L. Bhingare*

Marathwada Mitra Mandal's College of Pharmacy, Thergaon (Kalewadi), Pune -411033, India

***Corresponding author e-mail:** cbhingare@gmail.com

ABSTRACT

Fast dissolving drug delivery is the new approach to administer drugs; mouth dissolving film is one of them. The object of the present research work was to formulate a mouth dissolving film of Zolpidem tartrate from polymers Hydroxypropyl cellulose (EF-P) with a combination of Hydroxypropyl methyl cellulose K-15 by solvent casting method for enhancing the drug release rate and absorption to incessant increase drug bioavailability. Hydroxypropyl cellulose is a synthetic water soluble polymer, form a brittle film with high elastic modulus, thus to improve film forming properties, Hydroxypropyl methyl cellulose used in a ration of (1:1 and 2:1) with it. Compatibility of drug and polymers were studied by the IR spectrophotometer, any kind of interaction was not found. All the formulations were evaluated by different evaluation parameters and showed satisfactory results. Batches have uniformity in weight with a thickness of (0.930 mm), (98.3%) drug content and 100% drug release within 6 mins and films pH was reassembled with the pH of saliva.

Keyword: Hydroxypropyl methyl cellulose, Hydroxypropyl cellulose, Mouth dissolving film, Solvent Casting Method.

INTRODUCTION

Oral solid dosage forms are most preferred route for administration of drug by medical practitioners and manufacturer due to the highest acceptability of patients. [1] In some cases such as high first pass metabolism of drugs, lower bioavailability, long onset time and fear from the administration, dyspepsia condition turned to the manufacturer to develop a new drug delivery system. Some drug belongs to BCS class II and it's challenging to develop solubility enhancement strategies to increase oral bioavailability. [2] Some techniques have been developed to solve this problem including pro-drug, salt formulation, particle size reduction, inclusion complexes and change in solid dosage form. This objective led to the emergence of the concept of fast dissolving dosage form. There are number of dosage formed available like effervescent tablets, drug syrups and chewing gum tablets, mouth dissolving tablets which are commonly used to enhance the patient compliance but mouth dissolving tablets that can dissolve in the oral cavity have attracted a great deal of attention. [3] Now a day's mouth dissolving tablets are replaced by mouth dissolving films and have excellent efficiency to fulfill the entire patient as well as manufacture requirement. [4] Mouth dissolving films is the new dosage system for delivery of drugs through the oral cavity and was developed on the basis of the transdermal patch technology. The delivery system consists of a very thin oral strip, which when placed on the patient's tongue or any oral mucosal tissue gets instantly wet by saliva and rapidly hydrates. [5] In film dosage form, the drug is highly perverse, rapid drug absorption takes place with an instant increase in bioavailability and this leads to quick onset of drug action. [6] Bioavailability of drug is significantly greater than those observed from a conventional tablet dosage form because of film dosage form; the drug is directly absorbed at local and systemic circulation without undergoing first pass hepatic metabolism. [7] Hydrophilic polymers and plasticizer are the most essential and major component of mouth

dissolving films. [8] Hydroxypropyl methyl cellulose (HPMC) is known for its good film forming properties and has excellent acceptability; lower grades of HPMC like Methocel E_3, E_5, and E_{15} are particularly used because of their low viscosity. HPMC forms transparent, tough and flexible films from aqueous solutions. Hydroxypropyl cellulose (HPC) is non-ionic water soluble thermoplastic polymer, films of it were shown low mechanical strength, stiff, and very low percent elongation (less than 5%). [9,10] Thus to formulate quick mouth dissolving films which have good tensile strength, flexibility and thickness both the polymers was used in combination form.

MATERIALS AND METHODS

Materials: Zolpidem tartrate was received as gift samples. Hydroxy propyl methyl cellulose (K-15) and hydroxy methyl cellulose (EF-P) was received as a gift sample from Medley Pharmaceutical, Mumbai. Propylene glycol, Tween-80, Aspartame and menthol were purchased from Research lab Fine Chem. Industries, Mumbai.

Formulation method of mouth dissolving films: Different composition formulas were optimized as a primary film former for the formulation (Table 1). Aqueous solution of HPC and HPMC were prepared by dissolving in 50ml of hot water (80^0C) with continuous stirring to form a homogeneous solution, and then kept the solution for swelling of the polymer. Polyethylene glycol, Tween-80, citric acid, aspartame and flavours were dissolved in 10ml of distilled water. The drug was separately dissolved in distilled water. Both of these solutions were mixed in polymer solution with continuous stirring and kept for 2 hours for the removal of the air bubbles. Then the prepared solution was cast onto Petri dishes and kept in air dried, after that in hot air oven for 24 hours at 40 ^{0} c. The film was removed from the plate, cut 2cmX 2cm size.

Determination of infra red absorption spectrum:
IR absorption spectrum of HPC, HPMC and other excipients was recorded by Attenuated Total Reflectance (ATR) technique using IR Affinity-1 (MIRacle 10) Spectrophotometer, wherein 1-2 mg of drug sample was mixed with polymers and excipients. The resultant spectrum of the drug was compared with reference spectrum. [11]

Evaluation parameters of films
Appearance of films: Appearances in films were evaluated by visual observation such as transparent, semi-transparent and hazy**.**

Weight variation: Weight variations of the films were calculated by individually weighing selected films, and variation in weight was determined. [12]

Folding endurance: The number of times, film folded from the same place without breaking gives the values of the folding endurance. It was determined by repeatedly folding film at the same place till it broke or folded up**.** [13]

Thickness: Thickness of film was evaluated by using calibrated Vernier caliper. Three readings from all the batches were taken and mean thickness and SD was calculated. [14]

Surface pH: The surface pH of the film was determined in order to investigate the possibility of any *in-vivo* side effect. As an acidic or alkaline pH may cause irritation to the oral mucosa, therefore keep the film pH as close to neutral as possible. For this, the film was dissolved in 10 ml of distilled water and measured the pH by pH meter. The procedure was performed in triplicate and standard deviation was reported. [15]

Drug content: Films were dissolved in 100ml of pH 6.8 phosphate buffer solution, shake the solution till the film is completely dissolved, and then filtered it. From above solution, 1ml solution was diluted to 10 ml with same solvent, the absorbance was measured at 238nm using the placebo film as a blank solution and percent drug content was calculated.

In –vitro dissolution studies: Dissolution study was carried out in a USP basket type apparatus using the 400ml of 6.8 pH phosphate buffer as dissolution medium at 100 rpm and 37 ± 0.5^0 C temperature. 4ml aliquots were withdrawn at 30 sec time intervals up to 6 minutes and the same volume of fresh solution was added. The aliquots were diluted up to 10 ml with same solvent and absorbance was measured at 238nm, percent drug release was calculated. [16]

RESULT AND DISCUSSION

FTIR spectrum study: FTIR spectrum of physical mixture shows the compatibility of the drug with polymers and excipients. The characteristic peaks of drug are present at same wave number in physical mixture. This indicated there are not any kind of interaction happen between drug and excipients (Fig. 1).

Optimization of composition formulation and evaluation of films: Various composition formulas were composed to select the best formulation among

all. Effect of concentration of HPC and HPMC polymers and PEG on dissolution time was studied by formulating different composition formulation. To enhance the palatability of dosage form various combinations of sweeteners and flavours were studied. Batch F_1 and F_2 were composed to optimize the concentration of HPC in formulations. In F_1, (2:1) ration of HPC and HPMC were used, films were brittle, very low elasticity, sticky in nature, not easily peeled out and dissolve slowly, due to intrinsic properties of HPC. The combination of sweeteners and flavours were good in taste as compared to F_2 batch. In F_2, 1:1 ration of HPC and HPMC were used, the film has good mechanical strength, uniform thickness, less dissolution time and no residue found after dissolution. Hence ration of 1:1 of polymers was used for further studies. In F_3 and F_4 batch, concentration of PEG-400 was optimized to enhance the flexibility of films. Increase in concentration of PEG (F_3), flexibility of the film was improved but its drug release was decreased. The results of weight variation were found in the range from 35.927 to 48.462 mg. Uniform films thicknesses were observed in the range from 1.053 to 0.963 mm. That means by using a solvent casting method could prepare a uniform weight and thickness film. The value of folding endurance was observed 287.50 ± 4.654 in batch F_4, that means the film has sufficient mechanical strength and HPMC has improved the film forming property of HPC (Table 2). The pH of films was found near to the neutral pH, drug in remain unionized form after dissolution of film in saliva, which help with quick absorption of drug from oromucosal layer. All the formulations were evaluated to determine the drug content uniformity, 98% drug content was found, shown that the drug was uniformly dispersed in a polymer matrix (Table 3).

In-vitro dissolution study*:* The drug release profile of all the formulations was determined in phosphate buffer solution (pH 6.8). The drug release of formulation F_1 and F_2 were found to be 93.971% and 99.746% respectively within 6 minutes while the formulation F_3 and F_4 shown 97.213% and 100.991% Respectively within 6 minutes (Table 4). From the entire formulation batch, F_4 show comprehensive result and on the basis of evaluation data it was assured.

CONCLUSION

On the basis of investing results, it was concluded that the mouth dissolving film of zolpidem tartrate could be formulated by using HPC and HPMC polymers. The results of formulation F_4 matched with the required criteria, it has 98% drug content and maximum drug release within 6 mins. Hence this batch could be used for incessant release of drug, enhanced rate of absorption, efficiency and increase bioavailability.

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Table 1: Composition of Zolpidem Tartrate mouth dissolving films

Composition	Formulation code			
	F_1	F_2	F_3	F_4
Drug	50 mg	50 mg	50 mg	50 mg
HPMC-15	20 mg	25 mg	25 mg	25 mg
HPC (EF-P)	40 mg	25 mg	25 mg	25 mg
PEG-400	0.1 ml	0.1 ml	0.15 ml	0.1 ml
Aspartame	10 mg	8 mg	10 mg	10 mg
Sugar	25 mg	30 mg	30mg	25 mg
Citric acid	6 mg	6 mg	6mg	6 mg
Tween-80	0.1 ml	0.1 ml	0.1ml	0.1 ml
Colour, Flavoures	q.s	q.s	q.s	q.s
Water	q.s	q.s	q.s	q.s

Table 2: Evaluation of weight variation, thickness and folding endurance of mouth dissolving films

Formulation code	Weight variation (mg)	Thickness(mm)	Folding endurance (no. of folds)
F_1	39.311 ± 0.002	1.053±0.155	213.25±3.862
F_2	36.103 ± 0.002	0.936±0.025	245.00±3.365
F_3	48.462 ± 0.003	0.963±0.061	234.25±4.573
F_4	35.927 ± 0.001	0.930±0.026	227.50±4.654

All values are mean of 3 readings ± standard deviation

Table 3: Evaluation of drug content, surface pH of mouth dissolving films

Formulation code	Drug content (%)	Surface pH
F_1	96.962±0.559	6.933±0.152
F_2	97.407±0.339	6.666±0.152
F_3	98.300±0.780	6.733±0.115
F_4	98.518±0.462	6.800±0.100

All values are mean of 3 readings ± standard deviation

Table 4: Comparative *in-vitro* dissolution of formulation in pH 6.8 phosphate buffer

Time (Sec)	Formulation Code			
	F_1	F_2	F_3	F_4
30	11.768	13.213	17.657	18.324
60	26.540	30.702	26.546	29.435
90	34.680	38.213	36.568	37.680
120	41.657	43.124	42.146	46.524
150	50.680	52.591	49.657	53.946
180	58.613	60.613	58.457	59.724
210	64.457	68.168	63.880	66.546
240	73.213	75.124	73.346	74.768
270	80.880	79.168	82.013	85.657
300	86.546	88.391	86.902	92.546
330	90.971	92.124	91.985	97.508
360	93.971	99.746	96.213	100.991

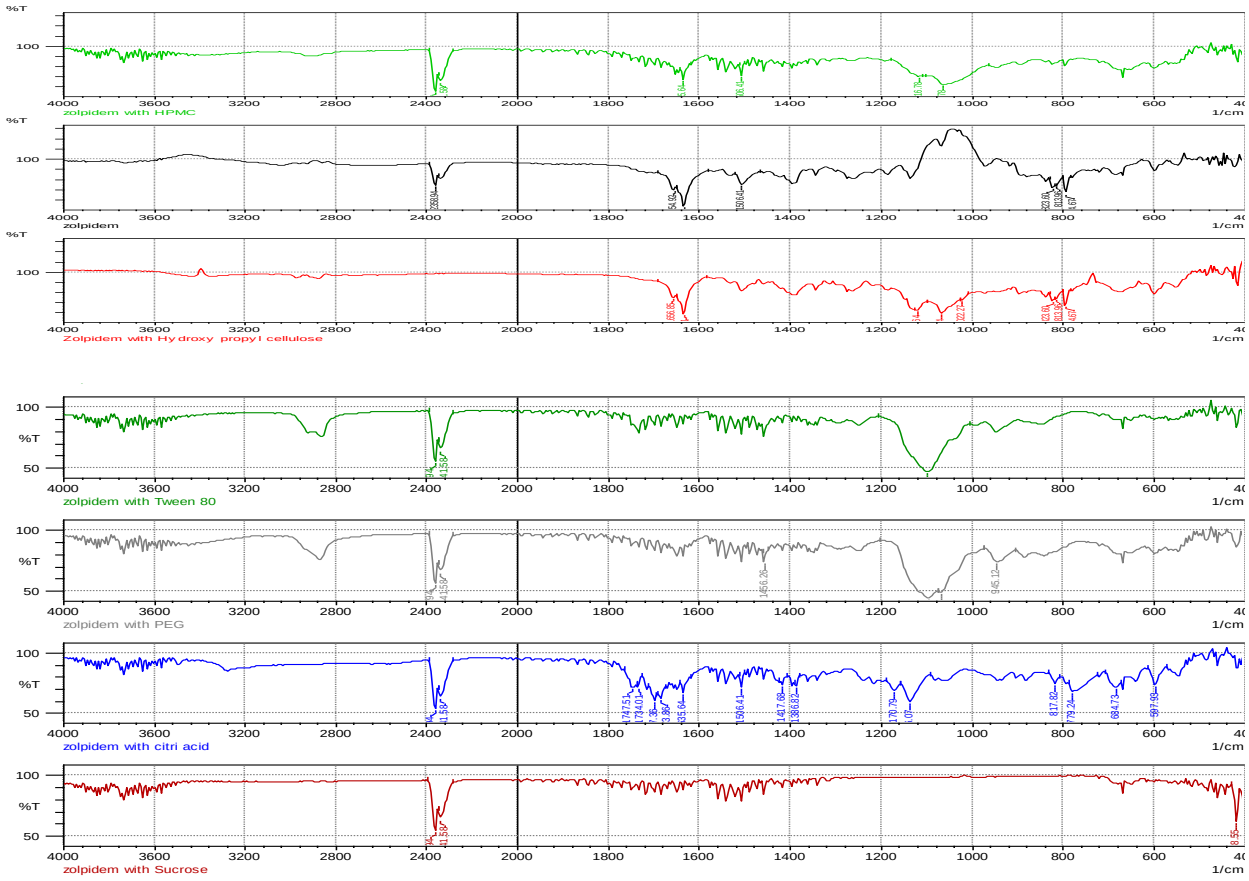

Figure 1: FTIR spectra of Zolpidem with polymers and other excipients

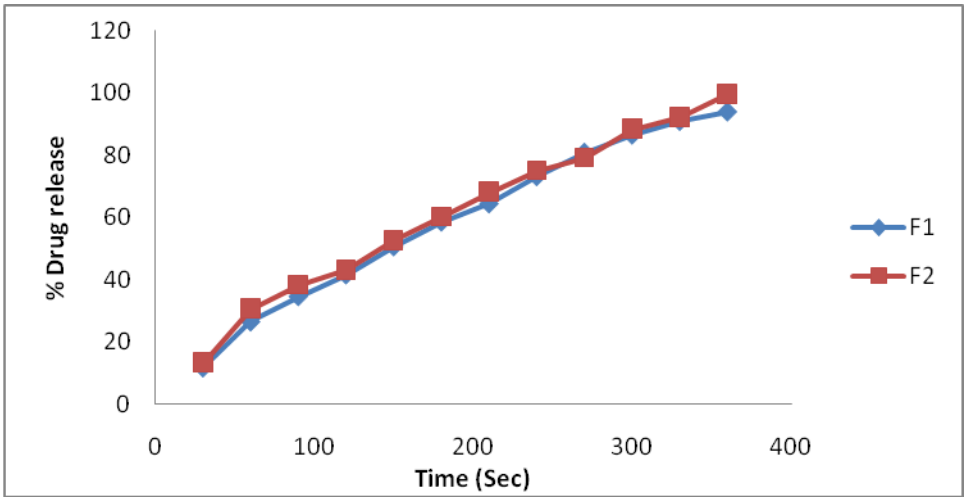

Figure 2: *In-vitro* drug release profile of formulation F_1, F_2

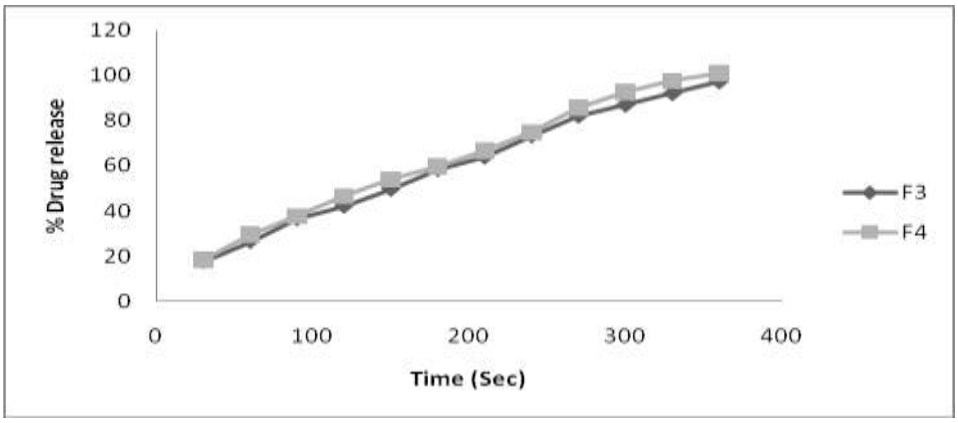

Figure 3: *In-vitro* drug release profile of formulation F_3, F_4

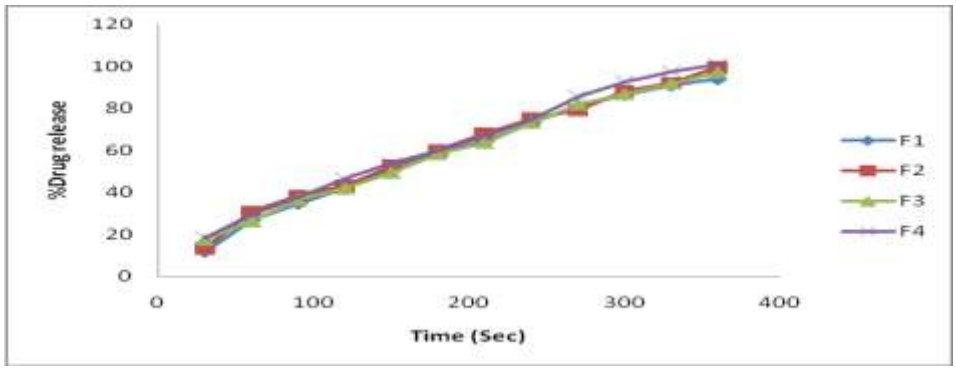

Figure 4: Comparison of *in-vitro* drug release of all formulation

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