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Formulation, characterization and invitro evaluation of loratidine oral thin films for rapid drug release.

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ABSTRACT

The purpose of the present investigation is to formulate fast dissolving oral films of Loratidine for the treatment of allergic rhinitis and urticaria. Films were prepared by solvent casting method using Natural Polymers Xanthan gum,GuarGum,SodiumAlginate,Aloe Vera Powder as the film forming polymer and PEG-400 as the plasticizer. Vanillin was used as taste masking agent in the formulations. Sodium Alginate has excellent film forming capacity with rapid hydration power which leads to rapid disintegration of film upon contact with saliva. The concentrations of the polymers and plasticizer were selected as independent variables. The observed independent variables were found to be most satisfactory formulation which demonstrates the feasibility of the optimization procedure in successful development of fast dissolving oral film containing loratidine by using Sodium Alginate, PEG-400 and Vanillin as key excipients.

Keywords: Xanthan gum, GuarGum, Sodium Alginate and Aloe Vera

INTRODUCTION

Overview on Fast Dissolving Oral Films

Oral route is the most preferred route for the delivery of the drugs till date as it bears various advantages over the other route of drug administration, but oral drug delivery systems still need some advancements to be made because of their some drawbacks related to particular class of patients which includes geriatric, pediatric and dysphagic patients associated with many medical conditions as they have difficulty in swallowing or chewing solid dosage forms. Amongst other factors, palatability of formulations of pediatric oral medications is one of the most significant factors influencing compliance to therapeutic regimens [1,2].

Although solid dosage forms are widely accepted by elders and adolescents, younger children tend to prefer liquid formulations that are easier to swallow [3]. Several novel technologies for oral delivery have recently become available to address the physicochemical and pharmacokinetic characteristics of drugs, while improving patient compliance. Electrostatic drug deposition and coating [4,6], and computer-assisted three-dimensional printing (3DP) tablet manufacture have also recently become available[5,6].

So, Fast-dissolving drug-delivery systems came into existence in the late 1970's as an alternative to tablets, capsules and syrups for pediatric and geriatric

patients who experience difficulties in swallowing traditional oral solid-dosage forms.

Research and development in the oral drug delivery segment has led to transition of dosage forms from simple conventional tablets or capsules to modified release tablets or capsules to oral disintegrating tablet (ODT) to wafer to the recent development of oral fast dissolving films (OFDFs). Amongst the plethora of avenues explored for the rapid drug releasing products, oral strip technology is gaining much attention [6,7]. (ODFT) was already popular amongst the people in the early 2000 year with the introduction and widespread use of Listerine pocket strips, a new launch in the mouthwash range.

Technology Catalysts forecasts the market for drug products in oral thin film formulations to be valued at $500 million in 2007 and could reach $2 billion in near future [7,8,18]. However only a few products consisting bitter molecules have been able to be commercialized because of the complexity associated with the ODT.

The United States provides the greatest market opportunity for fast dissolve dosage forms followed by Europe and Japan [9] as shown in fig. 2

Oral fast dissolving film (OFDF) is one such novel approach to increase consumer acceptance by virtue of rapid dissolution, self administration without water or chewing.The film is an ideal intraoral fast-dissolving drug delivery system, which satisfies the unmet needs of the market, is easy to handle and administer, maintains a simple and convenient packaging, alleviates unpleasant taste, and is straightforward to manufacture. The film is placed on the top or the floor of the tongue. It is retained at the site of application and rapidly releases the active agent for local and/or systemic absorption.The development of a fast-dissolving film also provides an opportunity for a line extension in the market place, a wide range of drugs (e.g., neuroleptics, cardiovascular drugs, analgesics, antihistamines, antiasthmatic and drugs for erectile dysfunction) can be considered candidates for this dosage form [7,10-16].

A large number of drugs can be formulated as mouth dissolving films. Innovative products may increase the therapeutic possibilities in the following indications [12,17].

- Pediatrics (Antitussives, Expectorants, Antiasthamatics)
- Geriatrics (Antiepileptic, Expectorants)
- Gastrointestinal diseases
- Nausea (due to Cytostatic therapy)
- Pain (Migraine)
- CNS (Antiparkinsonism therapy)

AIM & OBJECTIVES

Aim

The aim of the present investigation is to formulate and evaluate the fast releasing oral film taking Loratidine as a model drug. Loratadine is a derivative of azatadine and a second-generation histamine H1 receptor antagonist used in the treatment of allergic rhinitis and urticaria.

At present Loratadine is available in the form of tablets in the market. Patients are non co-operative with these dosage forms. Hence fast releasing oral film have become an important tool to improve the patient compliance.

Objectives

- To carry out the Pre-formulation studies of Loratadine
- To formulate Fast Dissolving film containing Loratadine
- To evaluate Weight variation, Thickness, Tensile strength, Folding endurance, Disintegration time, Content uniformity and In vitro dissolution studies.
- To perform the stability studies for the optimized formulation.

METHODOLOGY

Preparation of Loratadine by Solvent-Casting Method

The Oral fast dissolving films were prepared by dissolving strip forming agents and plasticizer in the distilled water, then solution was continuously stirred up to 4 hours on magnetic stirrer [9,10,12,26] and kept for 1 hour to remove all the air bubbles entrapped. Meanwhile, in the separate container remaining water soluble excipients i.e. sweetening agent, flavor and drug were dissolved with constant stirring for 45 min. When the stirring was over both the solutions were mixed together with stirring for another 1 hour on magnetic stirrer. Then the solution was kept stationary for 1 hour to let the foams settle down. The resulting formulation was casted on to a plate of

surface area 18 cm^2. It was dried for 24 hours at room temperature. The film was removed from the plate very carefully and observed for any imperfections. Film of area 6 cm^2 (2 X 3) was cut and stored in a butter paper covered with aluminum foil and stored in a dessicator.

Table no 1. Composition of Various Formulations

S.No	Ingredients (mg/film)	F1	F2	F3	F4	F5	F6	F7	F8
1	Loratadine	30	30	30	30	30	30	30	30
2	Xanthan gum	0.4	0.7	-	-	-	-	-	-
3	Guar Gum	-	-	0.4	0.7	-	-	-	-
4	Sodium Alginate	-	-	-	-	1.5	2	-	-
5	AloeVera Powder	-	-	-	-	-	-	1.5	2
6	PEG-400	20	20	20	20	20	20	20	20
7	Vanillin	2	2	2	2	2	2	2	2
8	Sodium Starch Glycolate	1	1	1	1	1	1	1	1
9	Sodium Saccharin	1	1	1	1	1	1	1	1
10	Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Evaluation of Fast Dissolving Oral Films

Weight uniformity test

The weights of the films were found to be in the range of 30±0.24mg to 51.47±0.63mg.

Physical appearance and surface texture

The observation by visual inspection of films and by feel or touch, suggests that the films are having smooth surface and they are elegant enough to see.

Thickness of films

The thicknesses of the films were in the range of to 0.051±0.007mm to 0.037±0.002mm. The results of average thickness of all films were summarized in table no.2..

Folding endurance

Folding endurance of the films was found to be in the range of 13.60±1.31 to 38.62±1.52.The results of average folding endurance of all films were summarized in table no.2.

Surface pH

The surface pHs of all the films were found to be neutral as there was no colour change in the litmus paper.

Drug content uniformity test

The drug content uniformity is performed by taking three films in each formulation trial and the average drug content was calculated. The results were found to be in the range of 97.56±0.31% to 98.90±0.26%. The results of average drug content of all films were summarized in table no.2.

Invitro disintegration test

The disintegration times of the prepared films were in the range of 8.33±0.57 to 12±1.73sec. The results of average disintegration time of all films were summarized in table no 2.

Table no 2. Evaluation parameters of Loratadine FDOF

Code	*Weight Variation in mg(n±SD)*	*Thickness in mm (n±SD)*	*Folding endurance (n±SD)*	*Surface PH*	*Drug content in %(n±SD)*	*Disintegration time in sec(n±SD)*
F1	*46.18±0.31*	*0.051±0.007*	*19±1.02*	*6.5± 0.5*	*97.63±0.10*	*12±1.1*
F2	*48.92±0.28*	*0.049±0.007*	*21±1.58*	*6.6± 0.8*	*97.85±0.40*	*10.66±0.57*
F3	*50±0.24*	*0.049±0.005*	*23±2.00*	*6.4± 0.3*	*97.56±0.31*	*12±1.73*

F4	*52.62±0.28*	*0.046±0.005*	*36.33±1.52*	*6.5 ±0.5*	*97.7±0.85*	*11±1*
F5	*49.70±0.96*	*0.039±0.005*	*32.60±1.39*	*6.7 ±0.8*	*8.13±0.55*	*9.66±1.52*
F6	*51.47±0.63*	*0.037±0.002*	*38.62±1.52*	*6.8 ±0.3*	*98.9±0.26*	*8.33±0.57*
F7	*51.15±0.04*	*0.043±0.005*	*13.60±1.31*	*6.5± 0.2*	*98.86±0.35*	*10.66±1.15*
F8	*52±0.38*	*0.04*	*14.6±1.41*	*6.6± 0.5*	*98.53±0.47*	*9.66±0.56*

n =mean of 3

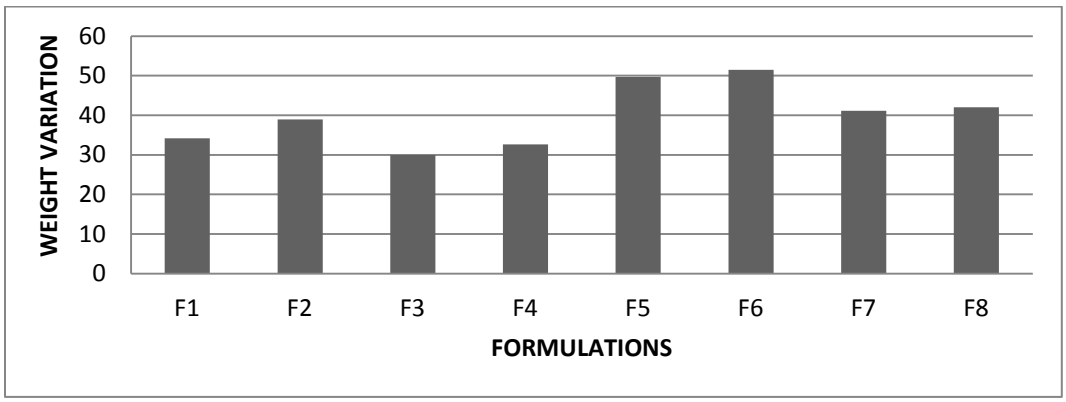

Fig.1.Weight Variation

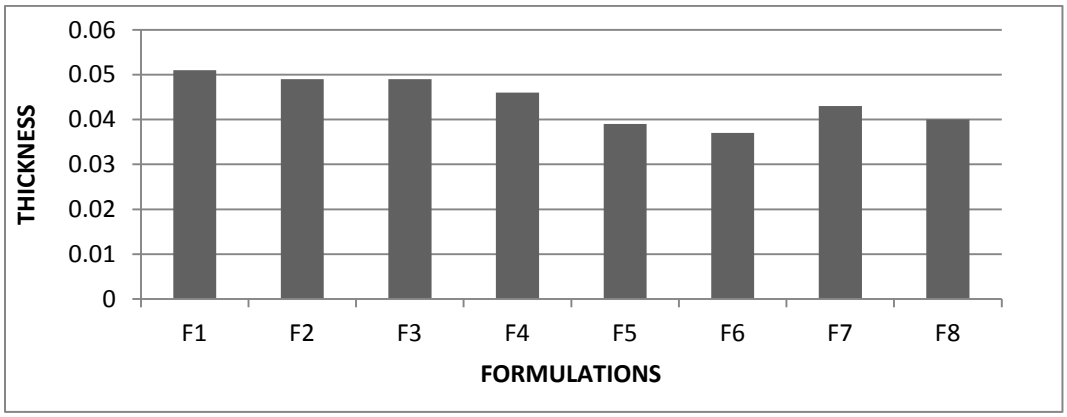

Fig.2.Thickness

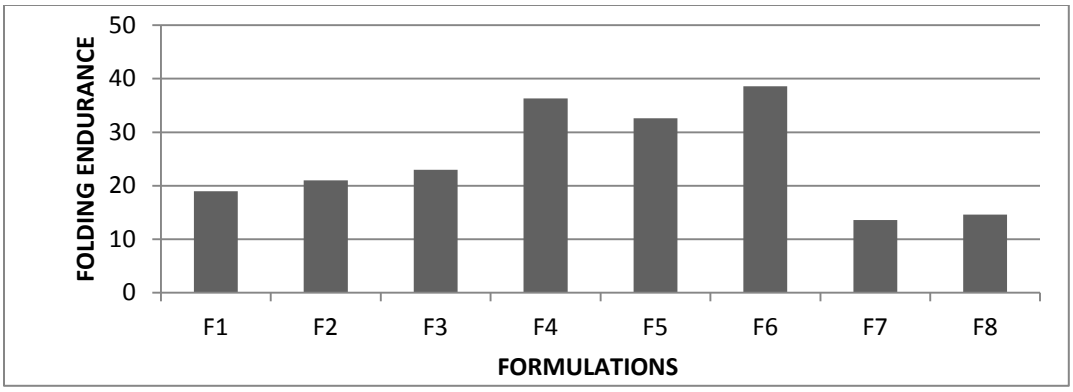

Fig.3.Folding Endurance

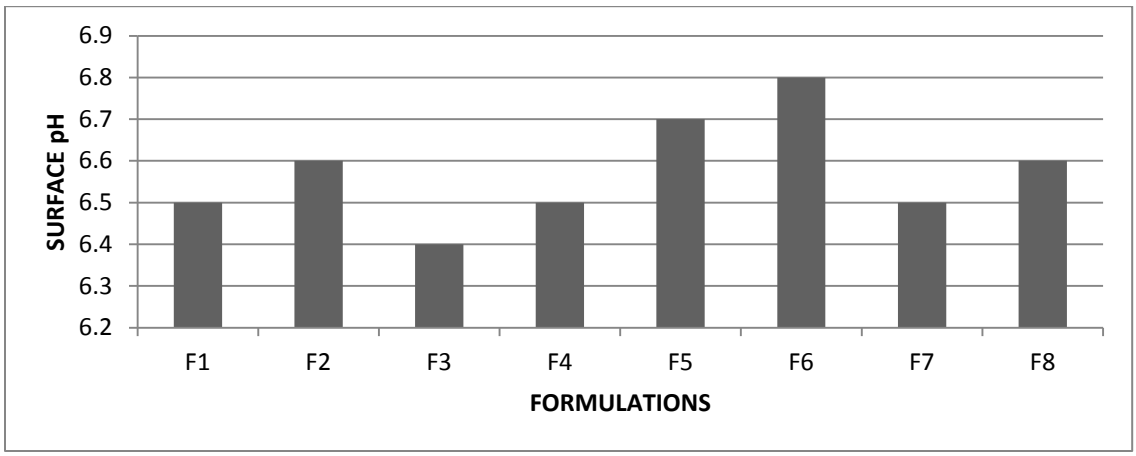

Fig.4.Surface pH

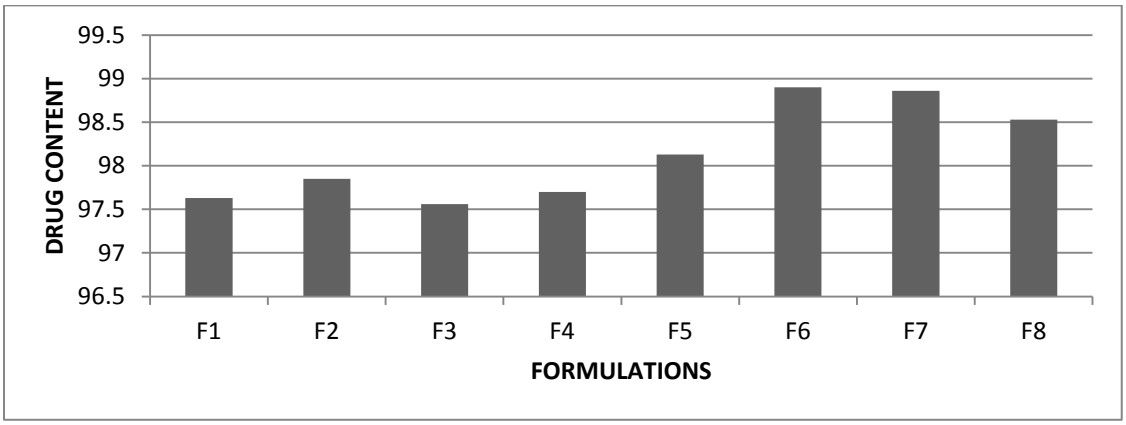

Fig.5.Drug Content

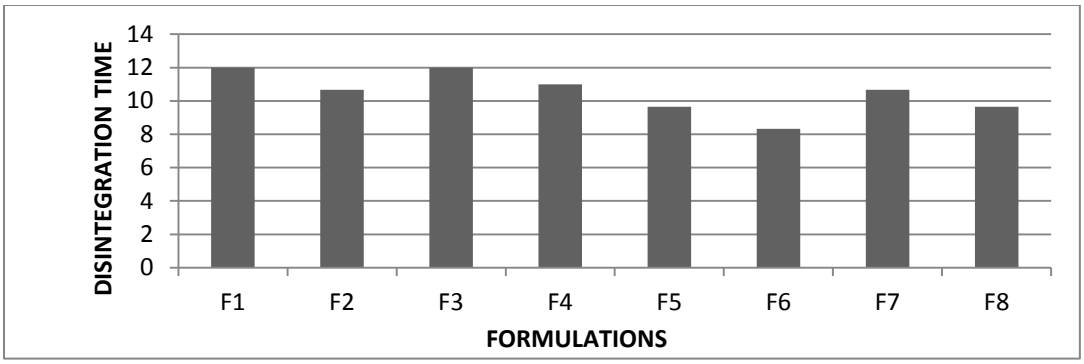

Fig.6.Disintegration Time

Invitro dissolution studies

Loratadine FDOF dissolution study was conducted in 6.8pH phosphate buffer solution as this was similar to the pH of simulated salivary fluid. A modified dissolution methodology was followed to simulate the conditions of the oral cavity. The dissolution volume consists of 300ml of 6.8pH phosphate buffer solution at 37±0.5˚C, which was rotated at 50rpm. Loratadine FDOF from each formulation was carried out in 6.8 pH phosphate buffer solution for 20min. The data of dissolution studies were summarized in table no.14 . The dissolution study was conducted for 20 min. The drug release was found to be in the range of 98±0.2 to 98.96±0.01%. and the % drug release was maximum. The plots of % cumulative drug release versus time (min) were plotted and depicted as shown in Fig.22. The formulation F6 showed higher drug release of 98.96± 0.01% revealing that films made with concentrations of Sodium Alginate and PEG-400 viz., 2%w/v was the optimized formulation as it shows a higher drug release in the dissolution study. As higher dissolution rate aids in faster onset of action, F6 was chosen as the optimized formulation.

Table no.3 .Invitro drug release data of formulation F1 to F8

Time in min	***% Cumulative drug release(%CDR)***							
	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
2	25.2± 0.81	22.2± 1.1	21.76± 0.66	20.53± 0.43	41.4± 0.01	38.56± 0.05	38.33± 0.37	34.16± 0.64
4	53.10± 2.05	45.33± 1.52	38.33± 0.37	38.56± 0.05	78.63± 0.11	72.6± 0.17	57.63±0.22	50.89± 0.41
6	76.60± 2.83	72± 1.01	56.52± 0.22	77.76± 0.81	98.3± 0.22	90.53± 0.24	84.13± 0.24	77.77± 0.81
8	92.33± 0.57	86.33± 1.52	81.56± 0.54	89.07± 0.16	-	98.96± 0.01	98.4± 0.17	89.07± 0.16
10	96.06± 0.25	91.33± 1.15	92.4± 0.89	94.86± 0.44	-	-	-	97.6 ±0.31
12	97.23 ±0.30	93.5 ±0.31	96.06 ±0.4	96.60 ±0.60	-	-	-	98.6 ±0.17
14	98.2 ±0.17	94.86 ±0.44	97.3 ±0.05	97.6 ±0.31	-	-	-	-

16	98.53± 0.31	95.96± 0.15	98± 0.2	98.3± 0.22	-	-	-	-
18	-	96.6 ±0.60	-	-	-	-	-	-
20	-	98.03± 0.05	-	-	-	-	-	-

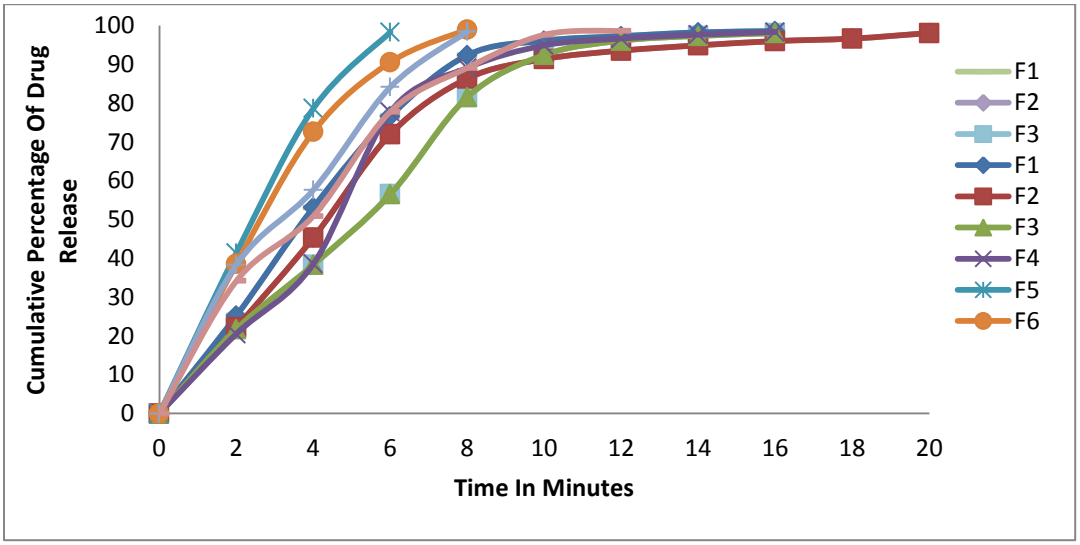

Fig.7. Invitro drug release data of formulation F1 to F8

Comparative Cumulative drug release of F6 with Marketed Product (CLARITIN)

Table no 4. Comparitive %Cumulative drug release of F6 with marketed CLARITIN

Time	F6	CLARITIN
2	38.56± 0.05	-
4	72.6± 0.17	-
6	90.53± 0.24	25.45±0.34
8	98.96± 0.01	32.12±0.86
10	98.96± 0.01	42.56±0.56
12	98.96± 0.01	50.67±0.43
14	-	58.35±0.87
16	-	63.25±0.32
18	-	69.9±0.35
20	-	75.16±0.76
22	-	82.56±0.45
24	-	88.67±0.75

26	-	92.67±0.23
28	-	95.54±0.34
30	-	97.4±0.23

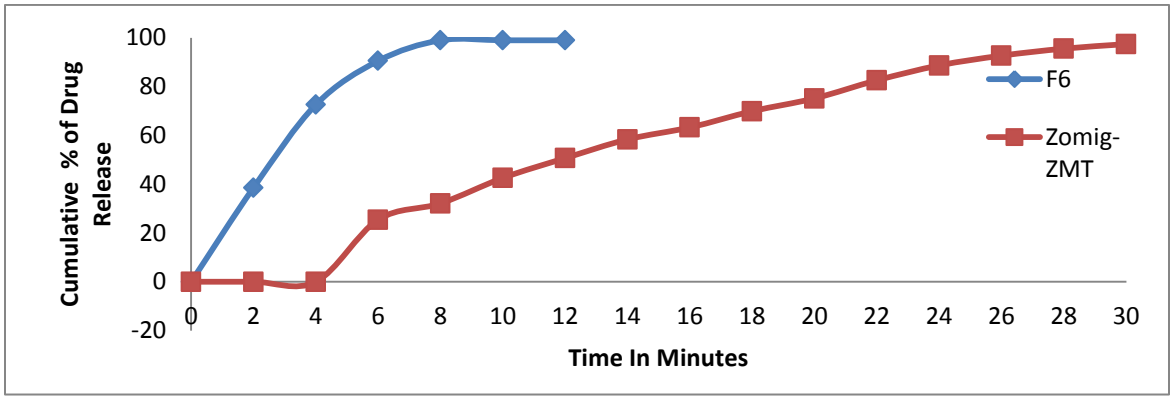

Fig.8. Comparitive Study of F6 with Marketed Product CLARITIN

Data analysis (Curve fitting analysis)

For analyzing the mechanism of the drug release kinetics of the dosage form, the data obtained were fitted to various kinetic equations of Zero order, First order, Higuchi model and Korsmeyer - Peppas model. The regression coefficient is calculated. Graphs of kinetic models were plotted with suitable data which was summarized. for First order release kinetics, for Higuchi release kinetics. forKorsmeyer-Peppas release kinetics. The First order plots.. The Higuchi plots. The Korsmeyer-Peppas The data of regression coefficient of different kinetic models were summarized

Curvefitting data ofdifferent kinetic models

The linear regression coefficient of each kinetic model was calculated and pattern of drug release from dosage form in predicted. The regression coefficients of First order plots, Higuchi and Korsmeyer-Peppas plots were higher when compared to zero order plots. The results are summarized in table no.5. Table no.5. Data of regression coefficient of different kinetic models

Formulation code	*Zero order* $(R)^2$	*First order* $(R)^2$	*Higuchi* $(R)^2$	*Korsmeyer-Peppas* $(R)^2$
F4	0.823	0.963	0.913	0.890
F5	0.972	0.899	0.970	0.985
F6	0.936	0.918	0.979	0.964

Stability studies

The formulation of F6 was evaluated for stability studies which was stored at 40˚C / 75% RH for 2 months and evaluated for their physical appearance, drug content and invitro disintegration time and % drug release at the end of 1st and 3rd month.The results were summarized in table no.6

Time in months	*Formulation F6 stored at 40˚C / 75% RH*		
	Physical appearance	***Disintegration time in sec***	***% Drug release***
Initial	Smooth & elegant	8.33±0.57	98.96± 0.01
After 1 month	Smooth & elegant	8.89±0.08	98.4±0.04
End of 3rd month	Smooth & elegant	9.24±0.25	98.1±0.05

DISCUSSION

Eight formulations were prepared. The thickness, folding Endurance, disintegration time, % drug released and drug content were selected as dependent variables. The optimized formulation, F6 was found superior than remaining 7 batches. Among all the formulations, F6 has shown maximum drug release of 98.96% within 8 min and a very low disintegration time of 8.33±0.57sec due to super-disintegrant Sodium Starch Glycolate. Hence the films made of 2%w/v of Sodium Alginate and PEG-400 showed excellent film forming property with rapid drug release profile. FT-IR studies revealed that there is no physicochemical interaction between polymer and drug. Stability studies revealed that optimized formulation was stable as the %drug release at the end of 3rd month was 98.1%.

CONCLUSION

In the present work, Loratadine fast dissolving films were prepared by Solvent Casting method using Natural Polymers and PEG-400. Loratadine is readily soluble in water but its bioavailability is low. It undergoes first pass metabolism. Hence it was formulated into FDOF to improve its bioavailability by avoiding first pass metabolism and in providing faster action in treatment. From the present study, it may be concluded that fast dissolving films of Loratadine can be prepared by solvent casting method using Natural Polymers as the film forming polymer. At 2%w/v of Sodium Alginate with PEG-400 showed the least disintegrating time of 8.33±0.57sec and the highest release of 98.96±0.01 % of the drug in 8min.

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