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FORMULATION AND *IN-VITRO* EVALUATION OF ORAL FAST DISSOLVING STRIPS BY USING EZETAMIBE AS A MODEL DRUG

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Abstract:
The oral mucosa is vascularized where by absorbed drugs get direct access to the systemic circulation without first pass metabolism. This present work is to formulate mouth dissolving film of Ezetamibe for enhanced bioavalibility. Drug and excipients studies were conducted using FTIR. Oral films of Ezetamibe were formulated using HPMC E5, as a film forming agent and propylene glycol as plasticize. And citricacid (salaviry stimulent), flavouring agents (vennila) are used.The solvent casting method was used for the preparation of films. Ezetamibe oral film was evaluated for folding endurance, thickness, weight variation test, surface pH, content uniformity,dissolving time and in-vitro dissolution. No drug–excipients interaction was observed. The characterization studies depict the purity of drug and all the excipients used in the formulation. The IR spectrum of mixture of Ezetamibe with all other excipients does not show any changes which indicate its compatibility with other excipients. From the results, it can be concluded that the fast dissolving oral film of Ezetamibe showed fast disintegration, dissolution of drug in salivary pH. Thus the prepared fast dissolving films of Ezetamibe could be a better alternative for achieving rapid oral bio availability.

Keywords: *Ezetamibe, hypercholesterolaemia,HPMC,*

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INTRODUCTION:

Oral delivery is the safest convineant and economical method of the drug delivery having the patient compliance. The fast dissolving drug delivery system was developed in the late 1970 [2] is an alternative like tablets, capsules and syrups for the children's (pediatric and gediatric patents then who experience difficulties in the swallowing oral solid dosage forms. The thin film is the drug delivery has been emerged advanced and alternative to the traditional tablets and capsules, and syrups like different dosage forms [1]. This drug delivery system have been advantages are like increased bioavalibility and to avoid the first pass effect most recently the fast dissolving films are gaining interests as an alternative to fast dissolving tablets. The fast dissolving films are disinterested with in 1-2 minutes when the placed in mouth without drinking water or chewing. The mechanism of action of oral films is when they are placed on the patient tongue, that films are instantly wet by saliva due to the presence of hydrophillic polymer and other excipients the film rapidelly hydrates and dissolves to release the medication for oral adsorption [4]. The oral fast dissolving films are often prepared by the solvent casting method and the hot melt method. The oral strips and oral films which rapidly dissolve under the tongue and buccle cavity. Could also improve the dissolution of poorly soluble in drug. Ezetamibe is Cholesterol is a type of fat (called a lipid). It is made naturally in your body from the food that you eat. When the concentration of cholesterol in your blood becomes too high, it is called hypercholesterolaemia. In people with hypercholesterolaemia, small fatty patches (called as hero ma) can develop within the inside lining of their blood vessels. Over time, these patches make blood vessels narrower, and this is called atherosclerosis, or 'hardening of the arteries'. This 'narrowing' reduces the blood flow through the arteries and it increases the risk of a number of heart and blood vessel diseases, such as heart attack and stroke [6]. Ezetimibe is a white, crystalline powder that is freely to very soluble in ethanol, methanol, and acetone and practically insoluble in water. Ezetimibe has a melting point of about 163°C and is stable at ambient temperature [7].

Type of medicine:-a lipid regulating medicine
Uses:-high blood cholesterol, Called as:-Ezetrol

MATERIALS AND METHODS:

Ezetimibe is the gift sample from Dr.reddys pharmaceutical inc.Hyd.and the polymers are hpmcE50Lv, k100m, E5, isopropyline, tween80, and propyleneglycol purchased from local market, Guntur, India.

Drug–Excipent Compatibility Study

Drug – excipent compatibility study was carried out using FTIR and DSC.Analysis of pure drug, excipent and physical admixtures of the drug with excipent were carried out using DSC.The temperature range room temperature to 200ºC.and FTIR.

Preparation of oral-fast dissolving films

The Polymer was weighed accurately and soaked in distilled water for 12hr. Soaked polymer was kept for the stirring for 10mins. Then the drug was weighed accurately and dissolves in satisfied amount of water along with 2 drops of tween 80 and propyleneglycol was added to the polymer solution while stirring. The stirring was continued until the bubble free dispersion was obtained. Then the dispersion was poured on to the filmformer and maintained the temperature set to the up-to 55ºC such that the dried film was obtained. The dried films were cut into the desired sizes and evaluated .The composition of film was mentioned in the table (1).

Method preparation

- The required amount of 2% HPMC E5 (2g) polymer was weighed and dispersed in the solvent mixture of water 100ml of water and add to the solution 2 drops of tween80 solution.then add into 0.1g of SSG.
- The required quantities of plasticizes and drug were added to the polymer solution and mix it to get clear solution. Then add 0.2g of drug and mix the solution.
- Then the bubble free solution &the clear solution was taken and poured into the filmfomer by the help of slab and dried up to 1 hr .the film after dried then remove and cut into the desired sizes.after the formulation was prepared.by using HPMCE50LV,K100M, E5 used Different polymer ratios.plasticizes are like isopropaline glycol and propyleneglycol as the dry polymer weight .Add 0.1mi citric acid using like salivery stimulent. The composition of the formulation was shown bellow the table (1).

Selection of polymer

Based on the literature review and the availability of the polymers, then after we have formulated blank films using three polymers like namely they are hpmce50lv, hpmce 5, k100m these polymers are the good film forming capacities.

Selection of formulation

The selection of formulation is based on through the films ware elegant the drug was found to get precipitated sate in the film containing hpmcE50Lvas shown in the figure…..(film pic)hence the film with HPMC-E5was considered as the best formulation as the drug is in free form and showed good drug

release.of the 4formulations ,F2is the considered as the best formulation.is the based on the various evaluation tests and *in-vitro* drug dissolution studies.

Final formulation

The final film formulation was preparation like various additives like sweetening agent, flavoring agent were dissolved in the small amount of water and added to the solution in the best formulation (F4) of all trail formulations (F1-F4)and the film was prepared using solvent casting method with in the following formula table(1)

Evaluation of prepared formulations.

The formulations were evaluated by the following tests.

1.Thickness

The thickness of a film can be measured by screw gauge at different locations (at least 4 locations). This is essential to determine uniformity and the thickness of the film as it relates directly to the accuracy of dose within the film.then the folding was noted and report it.

2.Weight variation

Take 20 films and then randomly selected from each formulation and the average weights various determined.

3.Folding endurance Test

The folding endurance was determined by the folding of the film at the same place(usually at the corner) repeatedly till the film brakes .the number of the times the film can withstand folds with out breaking is referred as the folding endurance value.

4.Drug content uniformity

5.The film of area 2x2 cm2 was cut and dissolved in little quantity of distilled water and 2ml of sodium hydroxide and the remaining volume was made up with distilled water to 100 ml in 100 ml volumetric flask. Then 1ml was withdrawn from the solution and diluted to 10 ml. The absorbance of the solution was taken at 238 nm and concentration was calculated. By correcting dilution factor,the drug content was calculated.

5. Dissolving time To be find the actual time to be required for the disintegration of the film dissolve the prepared into a suitable solvent or buffer and note down the values of the broken films.

6.*in-vitro* Dissolution test

The dissolution studies were carried by the using simulated saliva consisting of the acetate pHb4.5 buffer.to ascertains dissolution behavior of the film.

7.Surface PH of the film

The surface of the PH of the film was determined by using the PH meter. Cut the film into 2x2 cm^2. Then that the film was taken into a watch glass,moistered with the one drop of buffer and PH of the wet film was value was noted by using glass electrode in PH meter.

RESULTS AND DISCUSION:

In this study, an attempt has been made to design, formulate and evaluate the ezetamibe oral dissolving films by solvent casting method.

Standard calibration of Ezetamibe

The standard curve of Ezetamibe in the acetate 4.5pHbuffer was drawn by plotting the absorbance v/s concentration. The λmax of the Ezetamibe in the acetate buffer was determined to be 238nm.the absorbance values are tabulated in the table (2) standard calibration curve of the ezetamibe in the beers range between 2-10µg/ml is shown in figure1.

Drug -excipent compatibility study

Drug the excipent compatibility study was carried out using FTIR and DSC.the spectra of the pure drug and the final film were taken and it was taken and it was found as that the all peaks of the pure drug and polymer was not affected in the IR spectrum of the film and with respect to DSC, it was found that all the drug in the film was at molecular level.

The films are cut into small pieces and the weights were measured and average weights with standard deviation were reported in table no:-0.2and the final film formulation values are 4.7±0.2 to4.9±0.3.(mg/mean±SD) the thickness and uniformity content and folding endurance of all the films are within the limits. Thickness,wt variation, ,Dispersibility/Disintegration results were shown in table no:-02.thickness is 0.3±0.21 to 0.32±0.3mm(mean±SD),disintegration 0.9to10sec, folding endurance:-160±4.42 to161±4.42 (mean±SD).drug content uniformity values reported in table no:-03The main aim of formulating oral dissolving films was to attain fast dissolution of the particular drug within the 10 min.the required dissolution profile of the prepared films was required as the prepared ezetamibe films showed max drug release with in the 10 min.the dissolution profile of ezetamibe oral dissolving films was compared to that the market formulation.That the drug release was compares with that the marketed formulation.EZITROL 10 (Ezetamibe10g). pH of the film was measured and was found to be in the between4.2-4.5 for all formulations.

Table1: The formula for the final formulation is F2

INGREDENTS	F1	F2	F3	F4	F5
EZETAMIBE	0.2g	0.2g	0.2g	0.2g	0.2g
HPMCE5	1.5g	2g	2.5g	2g	2g
HPMCE50LV	1g	0	0	1g	1.5g
K100M	1.5g	0	1g	0	1.5g
SSG	0.1g	0.3g	0.5g	0.3g	0.1g
PROPALYINE GLYCOL	3ml	2.5ml	2ml	2ml	2.5ml
TWEEN 80	0.01ml	0.01ml	0	0	0
CITRIC ACID	0.5ml	0.5ml	0.25ml	0.25ml	0.4ml
MENTHOL	0.00ml	0.001ml	0.001ml	0.001ml	0.01ml
FLAVOURING AGENT	0.01ml	0.01ml	0.01ml	0.01ml	0.01ml

Table 2: Concentration Table

Concentration (µg/ml)	Absorbance
2	**0.191**
4	**0.341**
6	**0.621**
8	**0.821**
10	**0.991**

Fig.1: Standard calibration curve of Ezetamibe in acetate buffer pH 4.5

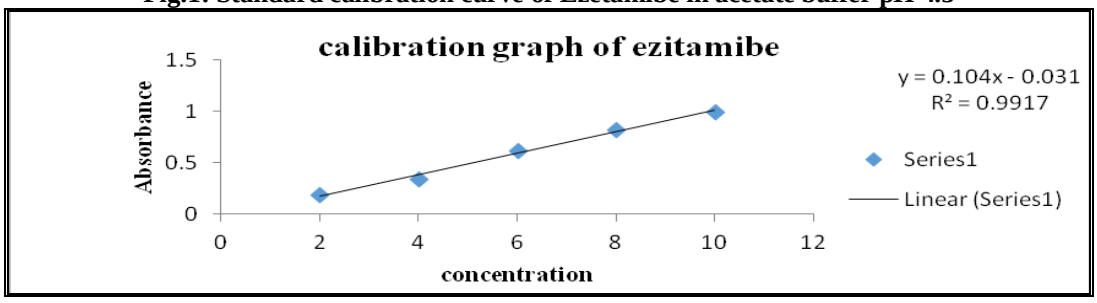


Table 3: Evaluation parameters

Formulation code	Thickness(mm) Mean±SD	Wt variation(mg)mean± SD	Folding Endurance mean±SD	Disintegration time(sec)mean±SD
F1A	0.31±0.02	4.6±0.3	170±7.23	15±0.43
F1B	0.34±0.05	4.9±0.3	169±6.93	13±0.99
F1C	0.39±0.06	5.2±0.3	170±7.23	16±0.22
F2A	0.3±0.021	4.9±0.3	160±4.42	1±.0.21
F2B	0.31±0.001	4.7±0.2	159±44.12	12±0.24
F2C	0.32±0.03	4.8±0.1	161±3.12	09±1.33
F3A	0.38±0.045	5.1±0.1	181±4.56	16±1.65
F3B	0.36±0.081	5.2±0.1	182±5.61	17±103
F3C	0.41±0.034	4.8±0.08	181±4.64	14±1.09
F4A	0.31±0.021	4.0±0.1	182±5.67	18±0.32
F4B	0.37±0.034	4.1±0.1	181±4.99	17±1.23
F4C	0.36±0.061	4.5±0.2	173±5.61	14±.34
F5A	0.35±0.034	4.7±0.3	171±5.43	13±0.51
F5B	0.34±0.044	4.4±0.3	169±6.55	12±1.98
F5C	0.32±0.48	4.6±0.2	171±4.88	16±0.98

Table4: %Drug Release Comparasion between Film and Tablet

TIME(sec)	FILM	TABLET
0	0	0
120	49.3	-
240	63.7	-
300	79.21	9.99
360	80.6	-
480	90.28	-
600	95.98	12.72
900	-	15.6
1200	-	19.9
1500	-	22.5
1800	-	29.4
2700	-	30.33
3600	-	60.22

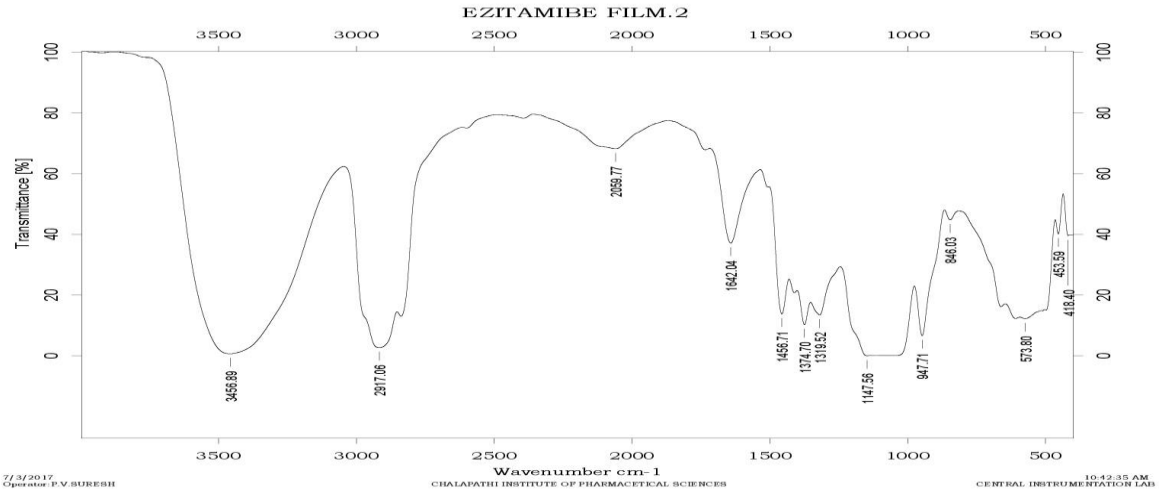


Fig.2: FTIR spectrum of Ezetamibe oral film.

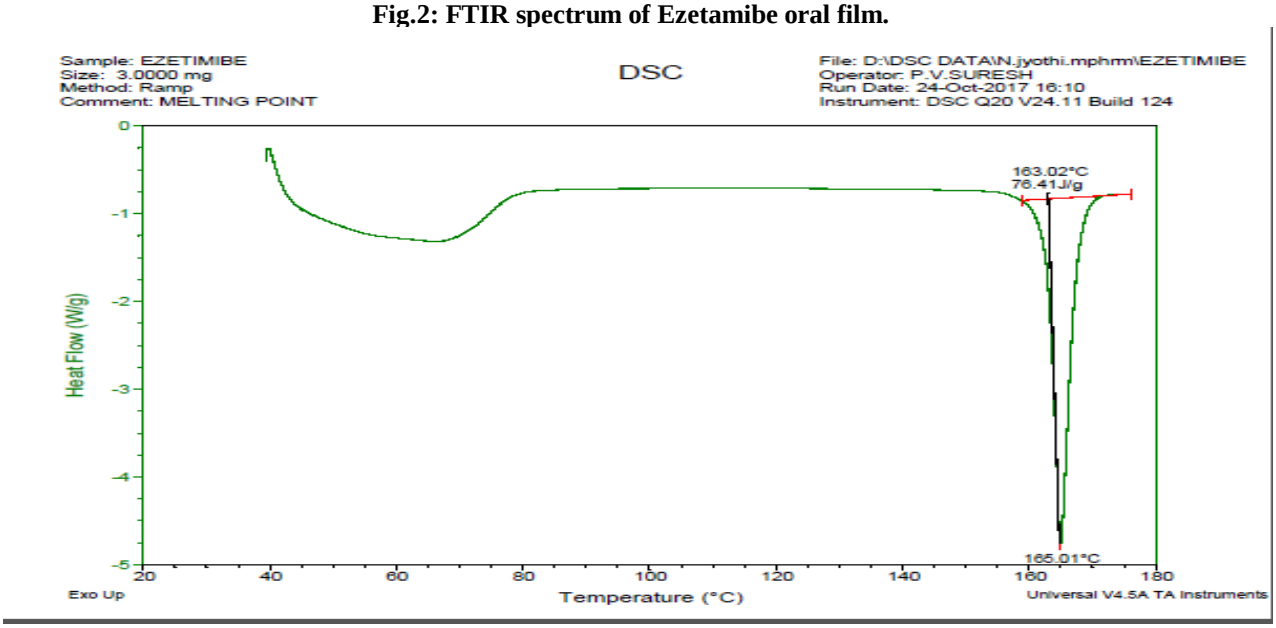
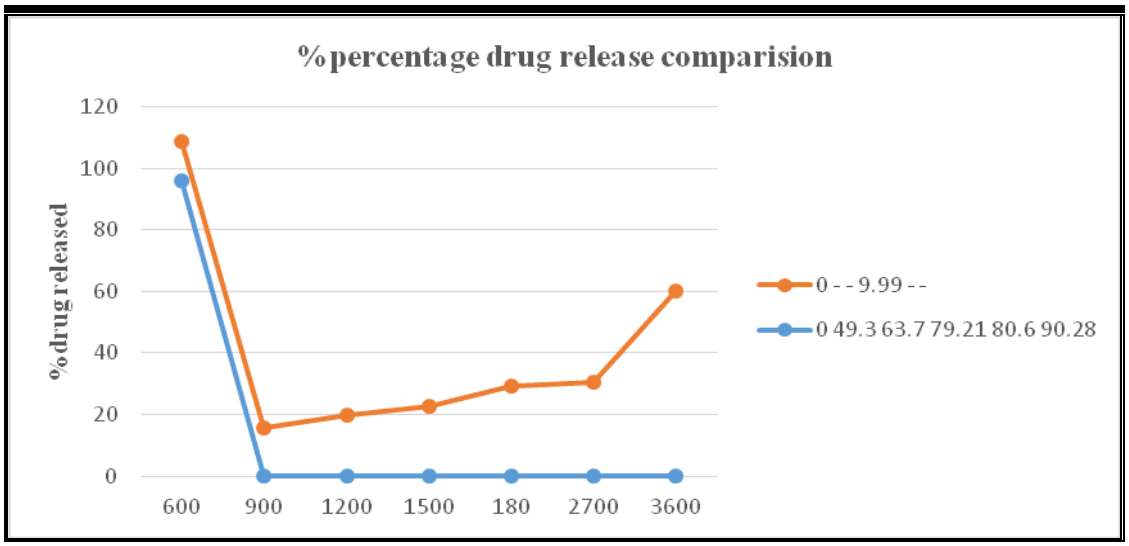


Fig.3: DSC Thermogram for film.

Fig.4: final film (F2)

Fig.5: (F4)



FILM; TABLET **Fig.6: % drug release comparison between film and tablet**

CONCLUSION:

The ultimate goal of any drug delivery system is the successful delivery of the drug, for the treatment of various disorders and diseases. Oral fast dissolving films are regarded as the safest, most convenient and most economical method of drug delivery having the highest patient compliance. In this the drug is dissolved or swallowed and then enters into the systemic circulation to produce the desired effect. Despite of as to advancement in drug delivery the oral route of drug administration is considered as the most important method of administration of drug for systemic effect because of self-medication, ease of administration and avoidance of pain compared to parenteral route. So the present work states that Ezetamibe can be effectively formulated as fast dissolving films with improved bio availability.

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