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Formulation Development and Evaluation of Mouth Dissolving Film of Ziprasidone Using Natural Bioenhancer

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ABSTRACT

The primary objective of this work was to develop a mouth dissolving film with Ziprasidone HCI, along with bioenhancer quercetin and basic ingredients like polymers, plasticizers, sweetener, saliva stimulating agent and flavor. The films were prepared by solvent casting I method. Quercetin enhances dissolution of drug which results in increase in % CDR upto 99%. HPMC E5 cps, which was not able to impart thickness to the film, HPMC E15 shown good flexibility. The plasticizer propylene glycol which was not able to impart flexibility and folding endurance to the film. PEG 400 produced good folding endurance, tensile strength and percent elongation. The optimized formulation (F3) was shown good mouth feel, folding endurance, instant drug release as well as good mechanical properties. The F3, shown less disintegration time of 31 seconds and 95% drug released within 3 minutes. Therefore it was concluded that rapid drug release was achieved for immediate onset of action using quercetin as natural bioenhancer which is beneficial and gives maximum drug release when compared to conventional dosage form.

KEYWORDS: *Ziprasidone HCL, bioenhancer, mouthdissolving oral film, solvent casting*

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INTRODUCTION

Due to ease of ingestion, avoidance of pain, versatility (to adapt to various types of drug candidates), and most importantly patient compliance and a strong drug delivery system, oral administration is the most popular route without sterility Conditions, so it is cheaper to produce. Recently, several new technologies for oral administration can be used to solve the physicochemical and pharmacokinetic characteristics of drugs while improving patient compliance. Electrostatic drug deposition and coating and computer-aided 3D printing (3DP) tableting are also available recently. The rapid dissolving drug delivery system was first developed in the late 1970s as an alternative to tablets, capsules and syrups for pediatric and elderly patients. Difficulty in swallowing traditional oral solid dosage forms. The new technology for fast-dispersing dosage forms is called fast-dissolving, fast-dissolving, fast-melting and fast-disintegrating tablets. However, the functions and concepts of all these dosage forms are similar. According to the definition, a solid dosage form dissolves or disintegrates rapidly in the oral cavity to forma solution or suspension without the need to administer water. It is called a fast-dispersing oral dosage form. Dysphagia (dysphagia) is common in all age groups, especially the elderly, and can also occur when swallowing regular tablets and capsules. Dysphagia is associated with many diseases, including stroke, Parkinsons disease, AIDS, thyroidectomy, head and neck thyroid therapy, and other neurological diseases, including cerebral palsy. The most common complaint is the size of the tablet, followed by the surface, shape and taste. The problem of swallowing tablets is most pronounced in elderly and pediatric patients, as well as those who travel frequently and do not have easy access to water.

Oral film is the latest technology in the production of oral disintegrating dosage forms. They are thin and elegant films of edible water-soluble polymers of various sizes and shapes (such as square, rectangular or disc). The stripes can be flexible or brittle, opaque or transparent. They are designed to break down

quickly on the tongue without the need for water. Fast disintegrating membrane (FDF) has a large disintegration surface area. These films alleviate the danger/fear of suffocation, they are easy to handle and administer, and they keep a simple and traditional container to manufacture, thus overcoming the short-lived failure of fast disintegrating oral tablets. The main limitations of these dosage forms are low drug loading and limited taste masking options. The fast-disintegrating film is a thin film with a thickness of 1-10mm and an area of any geometric shape with an area of 1-20cm2. The drug can be incorporated into a single dose of up to about 15 mg. The immediate dissolution in saliva is due to the special matrix made of water-soluble polymers, which usually has low viscosity and is easy to handle and apply. However, through wetting, the wet tack and mucoadhesive properties of the system are designed to hold the film at the application site. The flexibility and strength of the film are selected to facilitate the manufacturing process and processes such as rewinding, die cutting, and packaging. The rapidly disintegrating film is placed on the patient's tongue and mucous tissue, and it is immediately wetted by saliva. The film quickly hydrates and adheres to the application site. It then quickly disintegrates and dissolves to release the drug for absorption from the oral mucosa or for stomach absorption when swallowed.

1. EXPERIMENTAL WORK

1.1. PREFORMULATION STUDIES[22-25]

Pre-formulations can be described as the development phase that characterizes the physicochemical and biopharmaceutical properties of drugs. It is an important part of the drug development process. The information related to drug development obtained at this stage is used to make key decisions in the later stages of development. A variety of information must be generated to develop formulas reasonably. In the pre-formulation stage of product development, drug characterization is a very important step, followed by the study of the compatibility characteristics of excipients.

1.1.1. Organoleptic Properties:

The drug samples of Ziprasidone were studied for appearance, colour, odour and taste.

1.1.2. Melting point[30]

The melting point was determined by capillary method. The melting point was determined by introducing small amount of substance in the capillary attached to graduated thermometer and constant heat was supplied to the assembly suspended in the paraffin bath. The temperature at which drug melted was recorded. The melting point is reported in results section.

1.1.3. Solubility[26, 27]

The solubility of the selected drug was determined in distilled water, excess amount of drug added in water, solution was sonicated and centrifuged for 10 min and supernant was taken and analyzed by using double beam spectrophotometer. Solubility was reported in result section.

1.1.4. Ultraviolet-visible measurement

1.1.4.1. Determination of absorbance maxima (λ max)

The stock solution of Ziprasidone HCI was prepared in phosphate buffer pH 6.8, UV spectrum of 10 µg/ml solution of Ziprasidone HCI was taken to determine its absorption maxima (λ max) The results shown in section

1.1.4.2. Calibration curve of Ziprasidone HCL in Phosphate buffer 6.

1.1.4.2.1. Preparation of Phosphate Buffer 6.8

Accurately weighed 28.20 gm of disodium hydrogen phosphate and 11.45 gm of potassium dihydrogen phosphate was taken and dissolved in a small amount of distilled water, volume was adjusted to prepared 1000 ml phosphate buffer. The pH of the buffer solution was adjusted using pH meter.

1.1.4.2.2. Caliberation curve of Ziprasidone HCL in Phosphate Buffer 6.8

The stock solution was prepared with 10 mg Ziprasidone hydrochloride in 10 ml Phosphate buffer 6.8. Extract 10 ml from this stock solution and dilute to 100 ml with Phosphate buffer 6.8. Prepare the calibration curve by appropriately diluting the stock solution and using different concentrations (10 µg/ml-50 µg/ml). The absorbance is measured at 315nm.

1.1.4.3. FTIR Drug

The infrared spectra of pure Ziprasidone HCL were recorded by SHIMADZU 84005FTIR spectrometer equipped with a Interferometer dector. Sample were prepared by KBr disc method (2 mg sample in 100 mg KBr)and examined in the transmission mode. Each spectrum was measured over a frequency range of 4000-400[1]

1.2. Drug and Excipient Compatibility Study:

1.2.1. FTIR Study

An FTIR study was conducted to check the compatibility of the drug with the polymer. The infrared spectrum of Ziprasidone hydrochloride was measured on a Fourier transform infrared spectrophotometer using the KBr scattering method. Use dry potassium bromide for baseline correlation. Subsequently, an FTIR spectrophotometer was used to analyze the spectra of the drug, potassium bromide, and the dry mixture of the drug and various polymers. The maximum absorption in the spectrum obtained

with the test substance corresponds to the maximum absorption of the reference spectrum in position and intensity.

1.3. Formulation and development of Ziprasidone HCL Oral Film

1.3.1. Dose calculations

The drug to be loaded in the film was determined by dose of the drug and drug loading in petri plate was determined by the area of petri plate. Detailed calculation is included in section 10.3

1.3.2. Method of preparation

The water-soluble polymer and plasticizer are dissolved in distilled water. Stir the solution on a magnetic stirrer for 2 hours and set aside to remove all trapped air bubbles. At the same time, dissolve the excipients and drugs and fully stir for 30 minutes. After the stirring is completed, mix the two solutions. Finally, the solution is poured on a suitable petrochemical plate to form a thin film. The plate was kept in a hot air oven at 60°C for 1 hour. The dried film is gently peeled from the glass plate and cut to the required size.

Table 8: Formulation trials

Ingredients		F1	F2	F3	F4	F5	F6	F7	F8	F9
Ziprasidone HCL	(mg)	500	500	500	500	500	500	500	500	500
Quercetin	(mg)	0.125	0.125	0.125	0.125	0.125	0.125	0.125	0.125	0.125
HPMC E15	(mg)	1.0	1.25	1.5	-	-	-	1.25	-	1.25
HPMC E5	(mg)	-	-	-	1.0	1.25	1.5	-	1.25	1.25
PEG 400	(mg)	1.5	1.25	1.0	-	-	-	-	1.25	-
Propylene glycol	(mg)	-	-	-	1.5	1.25	1.0	1.25	-	-
Citric acid	(mg)	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10
Sodium Saccharin	(mg)	0.125	0.125	0.125	0.125	0.125	0.125	0.125	0.125	0.125
Flavor	(mg)	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15
Distilled water	(ml)	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs

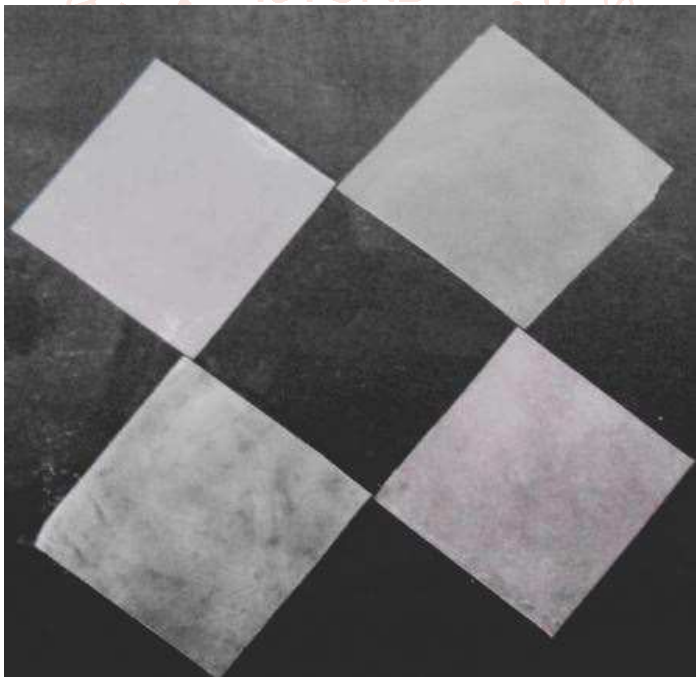


Fig 12: Fast Dissolving Films

1.4. EVALUATION OF ORAL FILM

1.4.1. Thickness[45]

Use a micrometer thread gauge to measure the thickness of the film. In order to obtain the uniformity of the film, the thickness was measured at 5 different places. The thickness of the film must be less than 5%.Weight variation Ten films were randomly selected and their average weight was weighed. Individual films were weighed and compared with the average weight for the deviation.

1.4.2. Folding endurance[47]

To determine the bending resistance, the film was cut and quickly folded in the same position until it broke. The number of times the film can be bent at the same position without breaking gives the value of the bending strength

1.4.3. Percentage elongation[48]

It was calculated by

$$\text{Percentage elongation} = \frac{\text{Increase in length of strip} \times 100}{\text{Initial length of strip}}$$

1.4.4. Tensile strength[49]

Tensile strength is the maximum stress applied to a point at which the strip specimen breaks. It is calculated by the formula

$$\text{Tensile strength} = \frac{\text{Load at failure} \times 100}{\text{Strip thickness} \times \text{strip width}}$$

1.4.5. In-vitro disintegration[50, 51]

Disintegrating time is defined as the time (sec) at which a film breaks when brought in contact with water or saliva.

Petri dish method

Put 2 ml of distilled water into a petri dish, add a film on the water surface, and measure the time for the oral film to completely disintegrate.

1.4.6. Weight variation

Ten films are randomly selected and their average weight is weighed. Weigh a single film and compare it with the average deviation weight.

1.4.7. Drug content[53]

The test is performed by dissolving a 4 cm^2 area film in 50 ml 0.1N HCl under stirring. Filter the solution using What man filter paper and dilute the filtrate to 100 ml with the same buffer in a volumetric flask. The solution was analyzed using an ultraviolet spectrometer.

1.4.8. In-vitro dissolution[52]

Use 900 ml 0.1N HCl as the medium and keep it at 37±0.5°C while setting the basket to 100 rpm. Cut a 4 cm^2 (2 x 2 cm) film sample and place it in the basket. Take 5 ml every 2 minutes and replace the same amount of samples with fresh 0.1N samples HCl. The extracted samples were filtered and analyzed using an ultraviolet spectrometer at a wavelength of 315 nm.

2. RESULTS AND DISCUSSION

2.1. PREFORMULATION STUDIES

2.1.1. Organoleptic Properties

The received of sample of Ziprasidone HCL was studied for organoleptic characters such as colour, odour and appearance. The results are reported in Table 9.

Table no 9: API characterization - Ziprasidone HCL

Test	Specification	Observation	Inference	
Color	off white powder	off white powder	Complies as per	IP
Odor	Odorless	Odorless	Complies as per	IP
Taste	Taste	Tasteless	Complies as per	IP
Melting Point	Range :215-219° c	217°c	Complies as per	IP

2.1.2. Melting point

The melting point was found to be at 217°c which is similar to melting point mentioned in IP.It indicates that the drug was in pure form.

2.1.3. Solubility

Solubility of the drug in water was found to be 0.00718 mg/ml.

2.1.4. Ultraviolet-visible measurement

2.1.4.1. Determination of absorbance maxima(λ max)

The absorbance maxima (λ max) was found to be 315 nm. The absorbance is measured at 315 nm is shown in Table 10 below. The absorbance maxima (λ max) of Ziprasidone HCL is shown in figure 13.

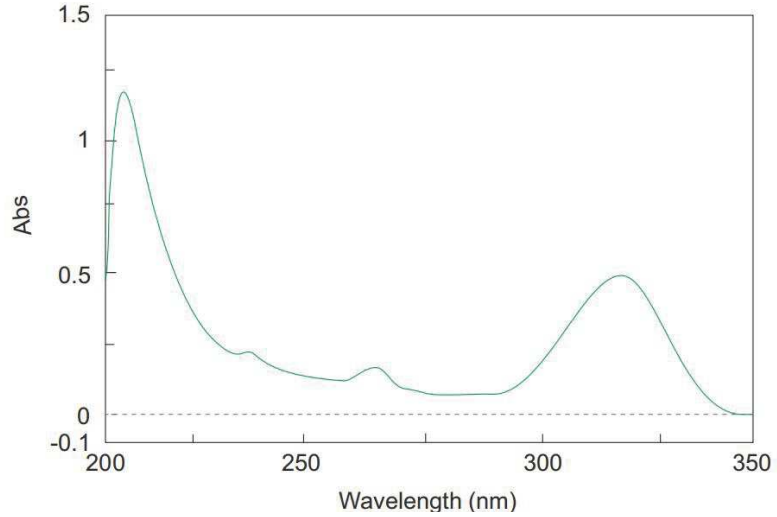


Fig 13: UV spectrum of Ziprasidone HCl

Sample Name: Ziprasidone HCL Peak Style Maximum Peak Range 350.0nm to 200.0nm Wavelength 315.0nm Abs 0.49.

2.1.4.2. Caliberation curve of Ziprasidone HCL in Phosphate buffer pH 6.8

Table no 10: Standard graph of Ziprasidone HCL

S. No	Concentration µg/ml	Absorbance (315 nm)
1	10	0.2357
2	20	0.4168
3	30	0.6215
4	40	0.8126
5	50	0.9562

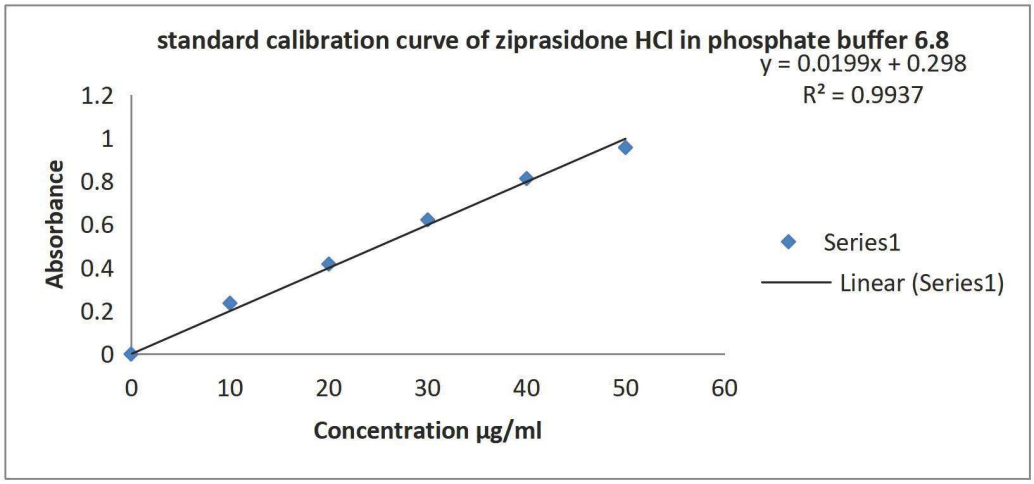


Fig 14: Standard graph of Ziprasidone HCL

From the calibration curve the regression equation was found to $y = 0.0199x + 0.0298$and $R^2 = 0.9937$ which will helpful in drug content and % CDR determination on UV spectrophotometer.

2.1.4.3. FTIR Drug

FT-IR study of Ziprasidone HCL was carried out to check the purity of drug. FTIR spectrum of Ziprasidone HCL is shown in Fig.No.15 and the interpretations of IR frequencies are shown in Table No.11

Table 11: Principal peak and functional group present FTIR spectra of Ziprasidone HCl

Functional Group	Reported Peak(cm -1)	Observed Peak(cm -1)
N-H Stretch	3300-3400	3352.49
C-H Stretch	2600-2650	2613.34
C=N	1700-1780	1742.49
C-N	1350-1400	1382.48
C-Cl	800-700	745.29

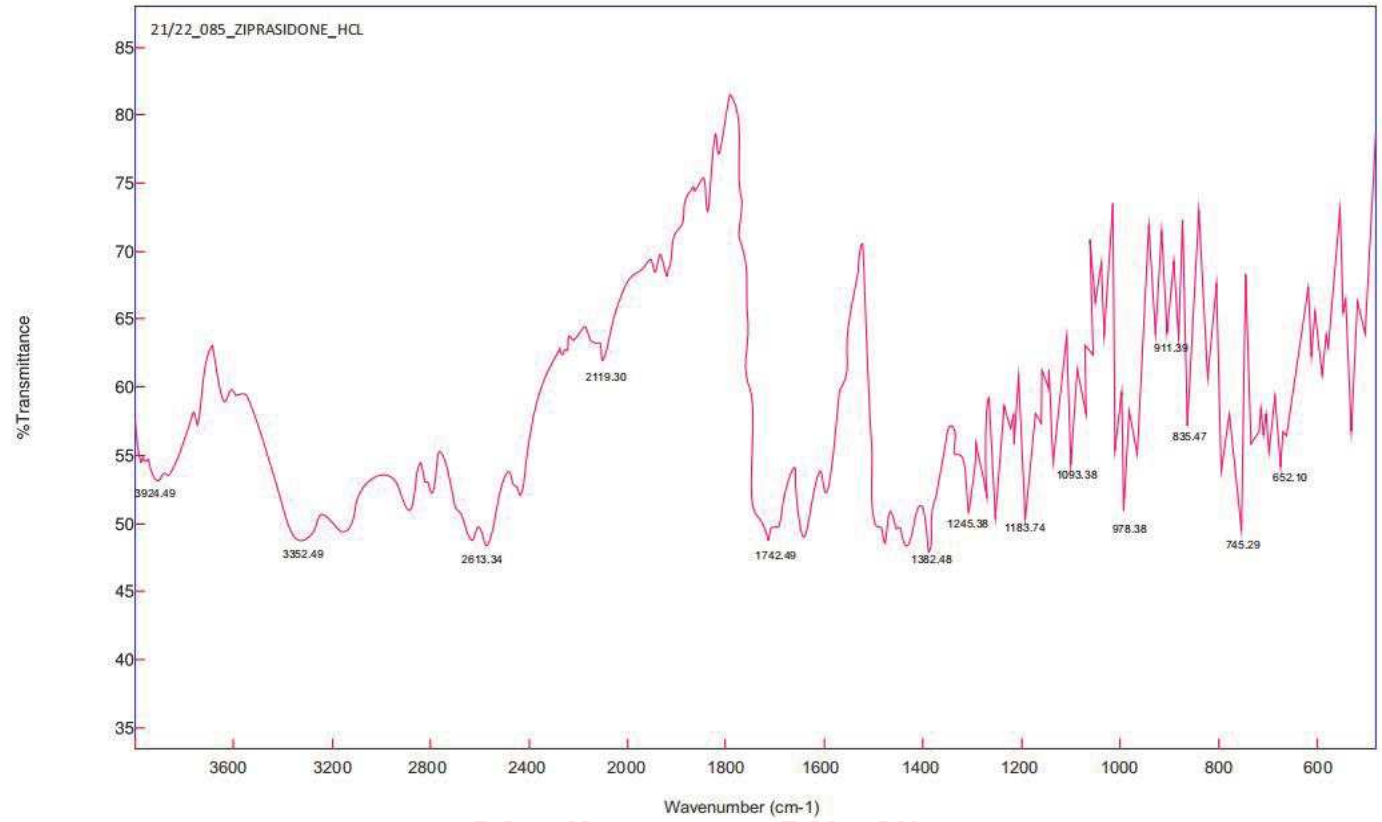


Fig 15: IR Spectra of Ziprasidone HCL

The observed peak and their functional group are given in Table 11. The IR spectrum(figure 15) of Ziprasidone HCL showed similar characteristics peak to that of reported IR spectrum of Ziprasidone HCL. From the FTIR study the sample was authenticated.

2.2. Drug excipients compatibility study

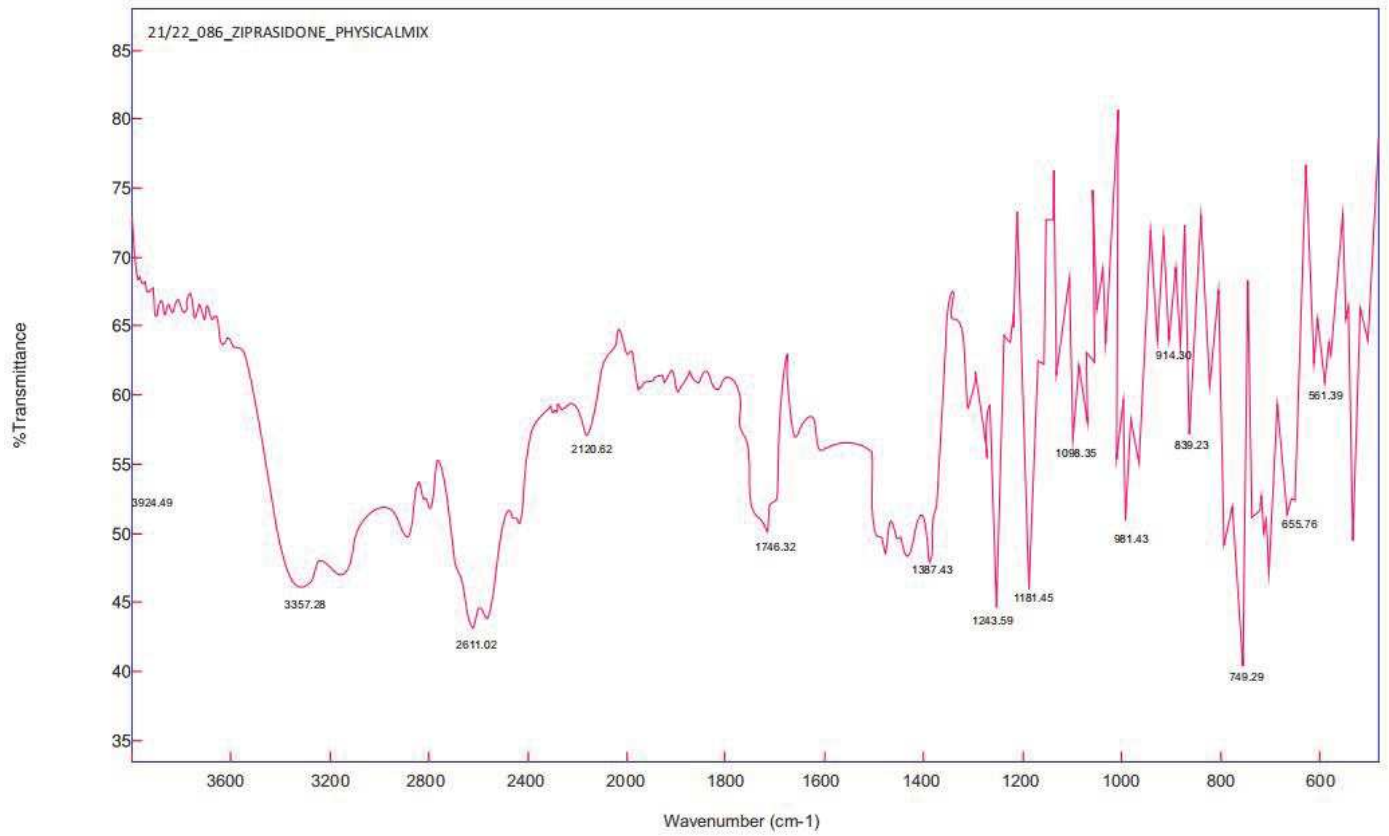


Fig 16: IR Spectra of Physical Mixture

Table 12: Interpretation of FTIR Spectrum of physical mixture

Functional Group	Peaks		
	Pure Drug	Physical	Mixture
N-H Stretch	3352.49	3357.28	
S-H Stretch	2613.34	-	
C=O	1742.49	1746.32	
C-H	1382.48	1387.43	
N=C=N	-	3357.28	

From the Infrared spectrometer it was found that all the principal peaks in Ziprasidone HCl is represent in FTIR of physical mixture; Hence it is concluded that no significant interaction was found in drug and excipients.

2.3. Formulation of oral films

2.3.1. Dose Calculation

Inner radius of glass plate = 5.65 cm.

Inner Area of the plate (πr^2) = 3.14 x 5.65 x 5.65 = 100 cm^2.

No. of 4 cm^2 films present whole plate =100/4 =25 films Each films contains 20 mg of drug.

25 films contain 500 mg drug (25×20). Labelled claim= 20 mg

2.4. Evaluation of Ziprasidone HCL oral film

2.4.1. Thickness

Use a micrometer thread gauge to measure the thickness of the film. In order to obtain the uniformity of the film, the thickness was measured at 5 different places. The thickness of the film must be less than 5% . From the evaluation of thickness of F1 to F9 batches was found in between 0.52 mm - 0.55 mm. Table 13 and Figure 17 show the thickness of the fast-dissolving film for all formulations.

2.4.2. Folding endurance

From the evaluation of Folding endurance of F1 to F9 batches was found in between 8 to 13 The folding resistance of the fast-dissolving film of all the formulations shown in Table 13 and Figure 17.

2.4.3. Percentage elongation

From the evaluation of % elongation of F1 to F9 batches was found in between 9 to 12. The percentage elongation of fast dissolving films of all formulations given in table 13 and figure 17

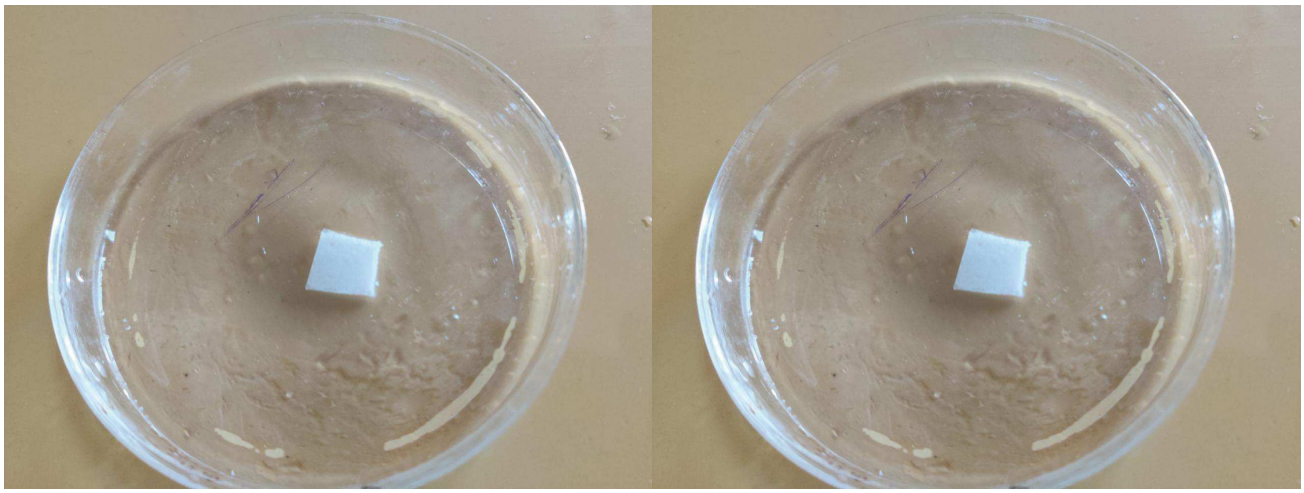
2.4.4. Tensile strength

From the evaluations of tensile strength of F1 to F9 batches was found in between 48.31 to 58.15 gm/cm^2. The tensile strength of fast dissolving films of all formulations given in table 13 and figure 17.

2.4.5. In-Vitro disintegration

Petri dish method

Put 2 ml of distilled water into a petri dish, add a film on the water surface, and measure the time for the oral film to completely dissolve.



From the evaluations of in-vitro evaluation of F1 to F9 batches was found in between 24 to 33 sec. The in vitro disintegration time of the fast-dissolving film of all formulations given in Table 13 and Figure 17.

Table 13: Evaluation parameters

Formulations	Thickness (mm)	Folding endurance	Tensile strength (g/cm2)	% elongation	In-vitro disintegration time (sec)
F1	0.54	12	53.15	10	28
F2	0.53	10	48.31	10	33
F3	0.52	9	55.1	10	31
F4	0.54	13	54.15	12	29
F5	0.54	10	52.01	9	32
F6	0.53	13	52.64	11	25
F7	0.55	8	58.15	12	24
F8	0.54	12	51.02	11	29
F9	0.53	10	49.61	12	31

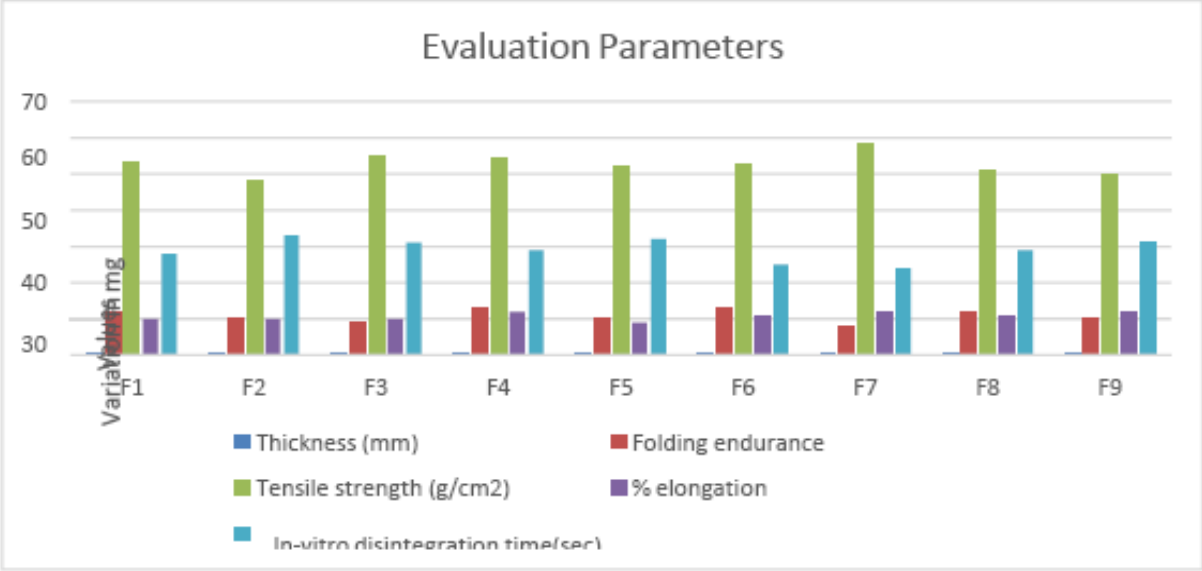


Fig 17: Bar chart of evaluation parameters

2.4.6. Drug content

The test is performed by dissolving a 4 cm^2 area film in 50 ml of Phosphate buffer 6.8 under stirring. Filter the solution using Whattman filter paper and dilute the filtrate to 100 ml with the same buffer in a volumetric flask. The solution was analyzed using an ultraviolet spectrometer. From the evaluations of Drug content of F1 to F9 batches was found in between 18.26 to 20.35 mg. The results of the drug content of all formulations shown in Table 15 and the values shown graphically in Figure 19.

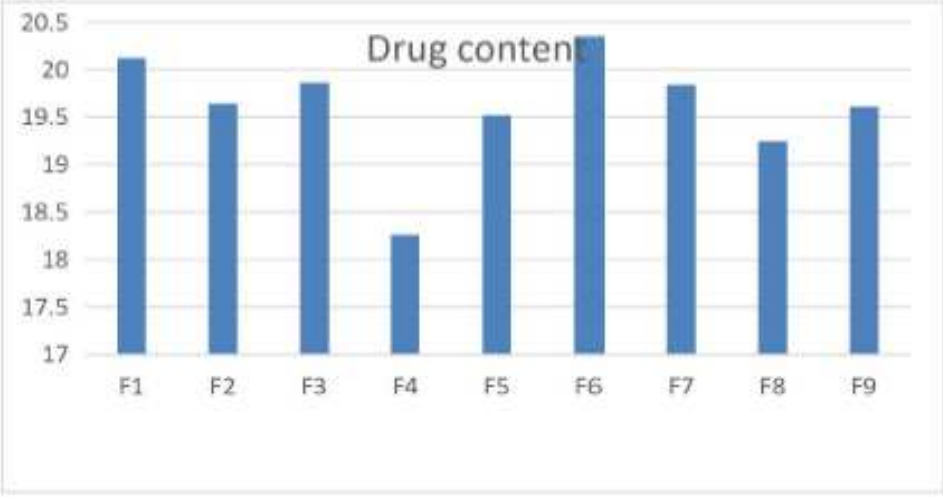


Fig 19: Bar chart of drug content

Table no 15: Drug content

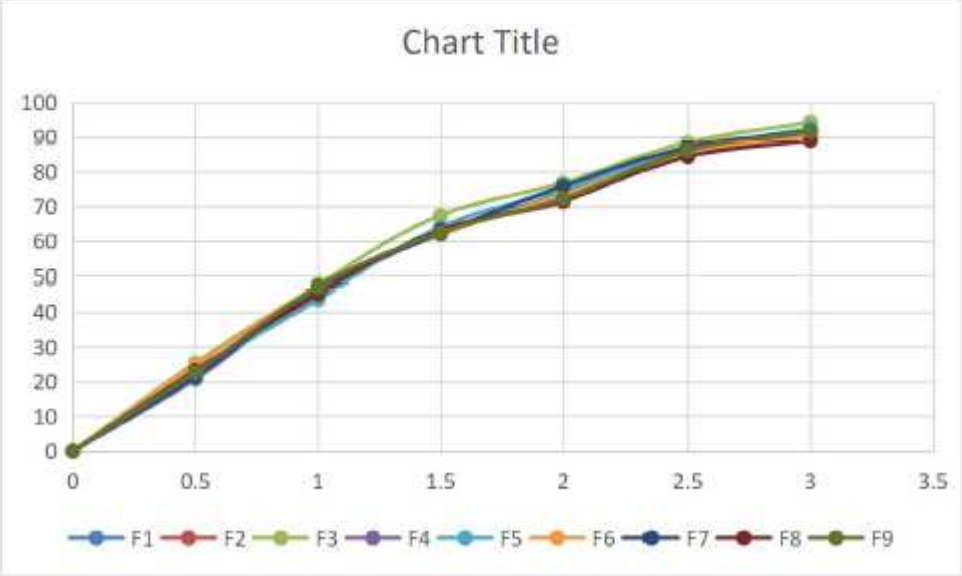
Formulations	Drug content(mg)
F1	20.12
F2	19.64
F3	19.86
F4	18.26
F5	19.52
F6	20.35
F7	19.84
F8	19.24
F9	19.61

2.4.7. In vitro dissolution

The in vitro dissolution profile data of all preparations are given in Table 16-24 and Figure 20-28. The cumulative drug release percentage of F1-F9 is shown in Table 25 & Figure 29. The in vitro dissolution profile data of the marketed formulations shown in Table 26 and Figure 30. The comparison of the in vitro release data of the commercial formulations and formulation 3 shown in the table 27 and Figure 31.

Table no 25: *In-vitro* dissolution of F1-F9 Percentage drug release

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
0.5	22.21	23.51	25.42	20.73	22.89	24.63	21.54	23.23	22.72
1	45.14	44.21	47.59	46.44	43.51	47.17	46.86	45.21	47.1
1.5	62.34	63.36	67.43	62.69	64.11	61.82	62.22	63.12	62.48
2	73.71	71.32	76.83	72.3	74.95	73.36	75.85	71.72	72.25
2.5	85.13	87.21	88.43	85.71	86.37	85.11	86.95	84.33	86.06
3	90.32	91.27	94.25	91.44	92.55	90.23	91.85	88.89	91.69



2.5. DISCUSSION

The present investigation was undertaken to formulate Ziprasidone HCL oral films forthe treatment of manic attacks and bipolar disorder.

F1-F3 were carried out with Quercetin, HPMC E15 cps, PEG 400, sodium saccharin, citric acid and flavor. The films were clear and transparent. The thickness also uniform. The flexibility also good. The films shown good mechanical properties. According to the assay result the drug was properly loaded in the film.

F4-F6 were carried out with Quercetin, HPMC E5, propylene glycol, sodium saccharin, citric acid and flavor. The films shows good appearance. The thickness alsonot uniform. The flexibility of the film was not good. The percentage drug release wasfound to be.

F7 was formulated with Quercetin, HPMC E15, propylene glycol, sodium saccharin, citric acid and flavor. The appearance of the film was also good but the thickness and disintegration time was more.

F8 was formulated with Quercetin, HPMC E5, PEG 400, sodium saccharin, citric acidand flavor. F9 was formulated with Quercetin, HPMC E15 & E5 without the addition of plasticizers. The formulated films were more brittleness.

Among all the formulations F3 shown good mechanical properties and less disintegration time of 31 seconds. All the parameters of film were found to be satisfactory. And the dissolution profile was found to be desirable and reproducible. The morphological study (SEM) of F3 shows more porous. Therefore rapid drug release was achieved for the immediate onset of action.

The stability studies were performed for about 1 month and 3 months. No significant changes were observed in the thickness, tensile strength, in-vitro disintegration and in-vitro drug release.

The film (F3) samples evaluated gave maximum release within 3 minutes indicating the rapid drug release profile which entails in faster onset of action for the medicament. Therefore the oral films have considerable advantage over the conventional dosage forms.

3. SUMMARY AND CONCLUSION

The primary objective of this work was to develop a mouth dissolving film with Ziprasidone HCl, along with bioenhancer quercetin and basic ingredients like polymers, plasticizers, sweetener, saliva stimulating agent and flavor.

The films were prepared by solvent casting method.

Quercetin enhances dissolution of drug which results in increase in % CDR upto 99%.

HPMC E5 cps, which was not able to impart thickness to the film. HPMC E15 shown good flexibility.

The plasticizer propylene glycol which was not able to impart flexibility and folding endurance to the film. PEG 400 produced good folding endurance, tensile strength and percent elongation.

The optimized formulation (F3) was shown good mouth feel, folding endurance, instant drug release as well as good mechanical properties.

The F3, shown less disintegration time of 31 seconds and 99% drug released within 3 minutes while the marketed formulation took 1 hour.

Therefore it was concluded that rapid drug release was achieved for immediate onset of action using quercetin as natural bioenhancer which is beneficial and gives maximum drug release when compared to conventional dosage form.

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