

## Use of Piperine as a Natural Bioenhancer in Formulation Development and Evaluation of Mouth Dissolving Film of Ziprasidone

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**ABSTRACT:** The most recent technology for creating oral disintegrating dose forms is oral film. Low drug loading and few options for flavour masking are these dosage forms' principal drawbacks.

The oral film is made up of different-sized and shaped ingestible water-soluble polymers. When a medicine is taken, it is released for either stomach absorption or oral mucosal absorption. Ziprasidone HCl, piperine, bio-enhancers, and other standard chemicals such polymers, plasticizers, sweeteners, saliva-stimulating agents, and flavours have been combined to create a mouth-dissolving film. The moment the film is applied to the patient's tongue and mucous tissue; saliva starts to spit on it. The film quickly absorbs water and sticks to the application place before immediately dissolving. The optimized formulation (F3) demonstrated good mechanical qualities, folding durability, and mouthfeel in addition to immediate drug release. The major goal of this study was to create a mouth-freshening film that dissolves in the mouth. The film (F3) samples that were tested had a rapid drug release profile, with the maximal release occurring in 3 minutes and a quicker start to the medication's action. The stability investigations took place for between one and three months. No significant changes were made to the drug release, in-vitro disintegration, thickness, or tensile strength.

**Keywords:** Absorption, Bioenhancer, Drug release, Mouth dissolving film, Ziprasidone.

### INTRODUCTION

More than 1% of people suffer from the terrible condition schizophrenia. Traditional antipsychotic drugs and more recent atypical pharmaceuticals are the two classes of medications used to treat schizophrenia (Syed and Braši 2021). A brand-new antipsychotic medication called ziprasidone has been given USFDA approval after both short-term and long-term efficacy studies. Ziprasidone has an inherent solubility of 0.3g/mL, which makes it poorly soluble and prolongs the time it takes for absorption. When food is present, particularly high-calorie fat cheese, its absorption rate doubles (Stroup and Gray 2018). But among patients with schizophrenia, compliance with such a dosage regimen is a major problem.

The oral route of drug administration is the most preferred route due to its ease of administration, non-invasiveness, patient compliance, and acceptability. Bioadhesive mucosal dosage forms including adhesive tablets, gels, and patches are outcomes of technological development. The use of polymeric films for delivering drugs into the buccal cavity has developed great potential (Pawar *et al.*, 2019).

Fast-dissolving films, a type of oral drug delivery system, was developed based on the technology of the transdermal patch. This delivery system consists of a

thin film, which is placed on a tongue or mucosal tissue, instantly wet by saliva; then it rapidly disintegrates a release the medication for oral mucosal absorption (Bilal *et al.*, 2020).

It is possible to create an oral drug delivery system that leaves little to no residue in the mouth after administration and has a pleasing mouthfeel. It can also facilitate the administration of drugs to mentally disabled and uncooperative patients, and help overcome the unacceptable taste of oral drugs (Alqahtani *et al.*, 2021).

Fast-acting drug delivery methods, including Mouth Dissolving Films (MDF), provide a practical method of administering medication. MDF is a new dose formulation that breaks down and dissolves within the mouth Quick action is made possible via intra-oral absorption, which also helps prevent first-pass effects (Patil *et al.*, 2014).

Patients with speech problems may be more accepting and compliant when using quick-dissolving drug delivery methods. FDDS will assist in managing the medication life cycle, particularly if the drug is a patent-protected product. Dose forms provide producers with more market exclusivity while offering more practical dosage forms or dosage schedules (Bala *et al.*, 2003).

The most recent technology for creating quickly dissolving dose forms is oral film. They are thin films made up of different-sized and shaped ingestible water-soluble polymers. When a film is applied to a patient's tongue or mucous tissue, saliva immediately wets the film (Sharma *et al.*, 2015).

The oral mucosa is the innermost layer of the ear, nose, and mouth. It contains a basal cell layer, which progresses to the surface through several differentiated intermediate layers. The cells are shed from the epithelial surface as they leave the mucosa (Groeger and Meyle 2019).

The mouth-dissolving films can be made using any one of the following processes, individually or in combination: rolling, hot melt extrusion, solid dispersion extrusion, solvent casting, semisolid casting, and rolling.

Evaluation of the film includes thickness, flexural resistance test, weight change, drug content, disintegration test, FT-IR, DSC studies, *in-vitro* dissolution test, and SEM analysis (Pereira *et al.*, 2020).

Piperine was used as an herbal enhancer for improving the bioavailability of curcumin. Piperine-based formulations have been delivered through several routes of administration, such as oral, topical, and parenteral. Several researchers filed US patents and European patents for the herbal ingredients associated with piperine (Kulkarni *et al.*, 2022; Pingale and Ravindra 2013).

Taste masking technique: In their original condition, many medications are unpleasant and unappealing. Drug interactions with taste buds have been avoided using physiological and physicochemical techniques. Alcohol, aldehydes, ketones, lactose, maltose, glycerol, and organic compounds all trigger the sweet taste receptors. The oral mucosa may become a buccal, sublingual, and mucosal route by using OTF. The treatment requires rapid absorption of priority administration methods, including those used to control pain and allergies. Orally Thin films (OTF) were developed by candy makers and oral care within a few years (Mishra *et al.*, 2011).

This study's primary goal is to increase patient compliance and obtain rapid onset to relieve symptoms of bipolar disorder by developing and evaluating formulas for preparing oral dissolution membranes using different concentrations of Ziprasidone, a drug for use in the treatment of mental health conditions such as schizophrenia and bipolar disorder.

## MATERIAL AND METHODS

**Materials:** Ziprasidone HCl monohydrate was obtained as a kind gift sample from Sun Pharmaceutical Industries Ltd, Vadodara, India, Piperine was extracted from *Piper nigrum*. Hydroxy propyl methyl cellulose (E5 and E15), propylene glycol, Polyethylene glycol 400, and Citric acid, we bought sodium saccharin from Himedia Laboratories Pvt. Ltd. in India. The formulation and analysis employed only HPLC and AR grades for all of the constituents.

## Methods:

**Preformulation studies:** The phase of drug development known as pre-formulations is where the physicochemical and biologic properties of the medication are specified. In later stages of development, important decisions are made using the information gathered at this point. The process of characterizing the drug is crucial, and then the compatibility properties of the excipients are studied (Patel *et al.*, 2014).

**Solubility:** The solubility of a powder is determined by its ability to be dissolved in different solvents, such as water and ethanol, determined at 20°C.

**Heavy metal content:** Comparing sample powder with a Lead standard solution at 10 ppm for 2 gm of a substance that has received the same level of exposure to air, water, and other highly contaminated elements in an industrial context allows for the determination of the amount of lead per million parts of powder.

**Melting point:** The melting point was established using the capillary tube technique.

### Ultraviolet-visible measurement:

**Determination of absorbance maxima ( max):** The absorption maxima ( max) of the stock solution of ziprasidone HCl at pH 6.8 and 10 mg/ml of UV radiation were measured (Nikhilitha and Pingale 2021).

### Calibration curve of Ziprasidone HCl in Phosphate buffer 6:

**Preparation of Phosphate Buffer 6.8:** Weighed precisely 28.20 gm and was dissolved in a little quantity of purified water. A 1000 ml phosphate buffer was generated after volume adjustments. Using a pH meter, the buffer's pH was adjusted (Varsha, 2022).

**Calibration curve of Ziprasidone HCl in Phosphate Buffer 6.8:** Ziprasidone hydrochloride, 10 mg, was dissolved in 10 ml of phosphate buffer to make the stock solution. 6.8 take 10 ml from this stock solution and phosphate buffer it to 100 ml. 6.8. By properly diluting the stock solution and using various concentrations (10 g/ml–50 g/ml), the calibration curve may be produced. At 315 nm, the absorbance is determined (Rajput *et al.*, 2021).

**Compatibility Studies:** Using the KBr scattering method and an infrared spectrophotometer with Fourier transform, the infrared spectra of ziprasidone hydrochloride were measured. The greatest absorption in the spectrum produced by the test chemical matches the maximum intensity and position of the reference spectrum absorption.

**FTIR spectra of the drug:** By using an interferometer detector and a SHIMADZU 84005FTIR spectrometer, the spectra of pure Ziprasidone HCl were captured. Samples were created using the KBr disc method (2 mg of material in 100 mg of KBr), and they were then analyzed using the transmission mode (Modi *et al.*, 2012).

### Drug and Excipient Compatibility Study using FTIR:

To determine whether the drug and the polymer were compatible, an FTIR study was carried out. Using a Fourier transform infrared spectrophotometer and the KBr scattering technique, the infrared spectra of ziprasidone hydrochloride were measured. Baseline

correlation should be performed using dry potassium bromide. The spectra of the drug, that of potassium bromide, and that of the dry mixture of the drug and different polymers were all analyzed using an FTIR spectrophotometer. The test substance's greatest absorption in the spectrum matches the reference spectrum's maximum absorption in location and intensity (Fadlelmoula *et al.*, 2022).

#### Formulation and development of Ziprasidone HCl Oral Film:

**Dose calculations:** The dosage of the medication and the area of the Petri plate were used to determine the drug to be placed into the film and the Petri plate, respectively.

**Method of preparation:** To create a thin layer, the solution is finally poured over an appropriate petrochemical plate. The plate spent an hour in a hot air oven set at 60°C. After being carefully removed from the glass plate, the dry film is trimmed to the necessary size. The method of preparation of the film is shown in Fig. 1.

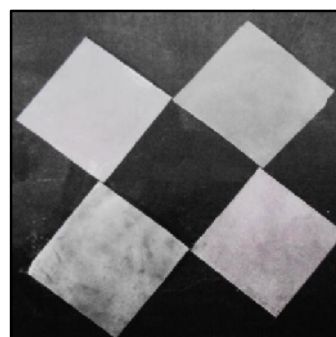


Fig. 1. Fast Dissolving Films.

The plasticizer and water-soluble polymer were dissolved in distilled water. To eliminate air bubbles, the mixture should be stirred on a magnetic stirrer for two hours before being placed aside. Dissolve the excipients and medications together, then mix thoroughly for 30 minutes. Mix the two solutions after complete stirring. The formulation trials are listed in Table 1.

Table 1: Formulation batches of Ziprasidone HCl Oral Film.

Ingredients (mg)	ZF1	ZF2	ZF3	ZF4	ZF5	ZF6	ZF7	ZF8	ZF9
Ziprasidone HCl	500	500	500	500	500	500	500	500	500
Piperine	2	2	2	2	2	2	2	2	2
HPMC E15	1.0	1.25	1.5	-	-	-	1.25	-	1.25
HPMC E5	-	-	-	1.0	1.25	1.5	-	1.25	1.25
PEG 400	1.5	1.25	1.0	-	-	-	-	1.25	-
Propylene glycol	-	-	-	1.5	1.25	1.0	1.25	-	-
Citric acid	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10
Sodium Saccharin	0.125	0.125	0.125	0.125	0.125	0.125	0.125	0.125	0.125
Flavour	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15
Distilled water (ml)	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

#### Evaluation of film:

**Thickness:** A micrometer thread gauge can be used to measure the film's thickness. The uniformity of the film was assessed by measuring the thickness at five different sites. Less than 5% of the film's thickness is required. Weight inequality the average weight of ten randomly selected films were determined. The variance was calculated by weighing individual films and comparing them to the average weight.

**Folding endurance:** The number of folds necessary to crack or break the specimen is how the folding endurance is measured. This demonstrates the fragility of the film. It was manually measured for the area of 3 cm<sup>2</sup> on the prepared film. In this experiment, the film was folded in the same plane repeatedly until cracks became visible on the film at the designated spot.

**Percent elongation:** Elongation-to-break measures the stress a material experiences just before it breaks (also known as ultimate elongation), and it provides a clue as to the material's toughness and stretchability before fracture.

**Tensile strength:** From the perspective of packing, the mechanical qualities of the film are crucial. To evaluate the strength and elasticity of the optimized film formulation, a tensile test was carried out.

**In-vitro disintegration:** A 3 × 3 cm<sup>2</sup> film was used for the disintegration test, which was conducted in a glass

Petri dish with 20 ml of water. The mixture was mixed after every 10 seconds. The duration of the film's breakdown was timed, and the results are shown as the mean of six determinations. Using a calibrated pH meter and a 3 × 3 cm<sup>2</sup> piece of film dissolved in 4 ml of water, the pH of the film was determined.

**Weight variation and content uniformity test:** The films of size 3×3 cm<sup>2</sup> that contain the drug dose were cut and weighed using an analytical balance to account for weight variance (Shimadzu Corporation Japan AUX 220). The films of size 3 cm<sup>2</sup> were cut from various points of the cast film for the content uniformity test. Each 9 cm<sup>2</sup> film was processed using ultrasonography for 15 minutes after being placed in a volumetric flask with 60 ml of pH 6.8 phosphate buffer. The volume was increased to 100 ml after the requisite dilutions, and the solution's absorbance was measured by a UV spectrophotometer at 315 nm.

## RESULTS AND DISCUSSION

#### Preformulation studies:

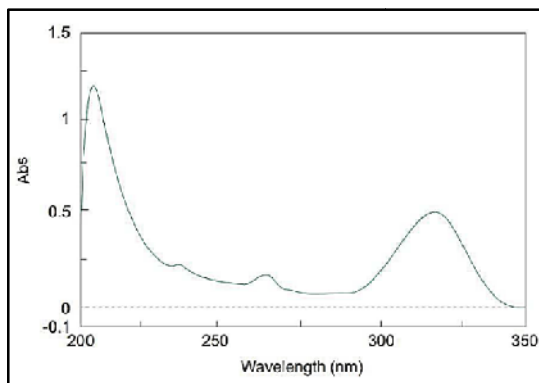
**Organoleptic Properties:** Organoleptic properties of the ziprasidone HCl sample, such as colour, odour, melting point, and solubility. Table 2 represents the findings of organoleptic properties of Ziprasidone HCl.

**Table 2: Organoleptic properties of Ziprasidone HCl.**

Test	Specification	Observation	Inference
Color	Off white powder	Off white powder	Complies as per IP
Odour	Odourless	Odourless	Complies as per IP
Taste	Taste	Tasteless	Complies as per IP
Melting Point	Range: 215-219°C	216-218°C	Complies as per IP

**Solubility:** Ziprasidone HCl was found to dissolve at a rate of 0.00819 mg/ml in water.

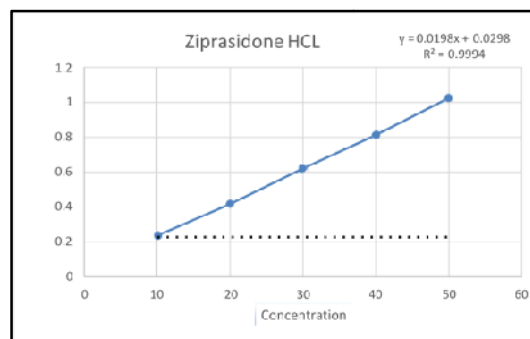
**Determination of absorbance maxima ( max):** It was determined that the maximum absorbance (max) was 315 nm. The observed absorbance at 315 nm is shown in Fig. 2.



**Fig. 2.** UV spectrum of Ziprasidone HCl.

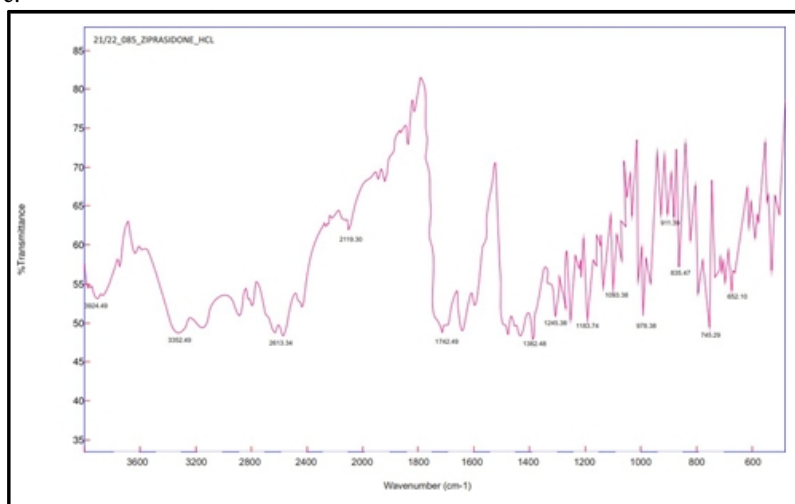
**Calibration curve of Ziprasidone HCl in Phosphate buffer pH 6.8:** Ziprasidone hydrochloride, 10 mg, was dissolved in 10 ml of phosphate buffer to make the stock solution. 6.8 Dilute 10 millilitres of this stock solution with 100 millilitres of phosphate buffer. 6.8. By properly diluting the stock solution and using various concentrations (10 g/ml–50 g/ml), the calibration curve can be created. The absorbance is calculated at 315 nm. Fig. 3 displays the Ziprasidone HCl standard curve.

The regression equation was discovered from the calibration curve to be  $y = 0.0198x + 0.0298$  and  $R^2 = 0.9994$ , which will be useful in determining drug content and % CDR on a UV spectrophotometer.



**Fig. 3.** Standard calibration curve of Ziprasidone HCl.

**FTIR of Ziprasidone HCl:** Using the KBr scattering and a Fourier transform infrared spectrophotometer technique, the infrared spectra of ziprasidone hydrochloride were measured. To determine whether the medication and polymer were compatible, an FTIR research was undertaken. For baseline correlation, use dry potassium bromide. The quality of the medication Ziprasidone HCl was examined using FT-IR technology. The FTIR research was used to validate the sample. Fig. 4 displays the FTIR spectrum of ziprasidone hydrochloride.



**Fig. 4.** FTIR Spectra of Ziprasidone HCl.

**FTIR for Drug excipients compatibility study:** Using the KBr scattering method and an infrared spectrophotometer with Fourier transform technique, the infrared spectra of ziprasidone hydrochloride were measured. To determine whether the medication and

polymer were compatible, an FTIR research was undertaken. The greatest absorption of the reference spectrum matches the maximum absorption of the spectrum obtained with the test material.

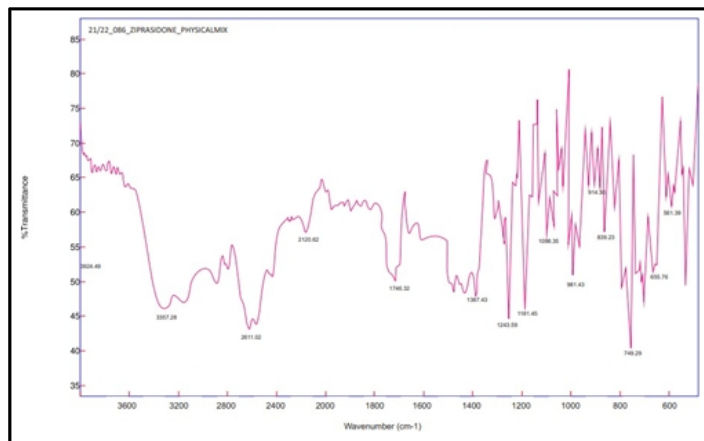


Fig. 5. FTIR Spectra of Ziprasidone HCl and Polymer (Physical Mixture).

**Preparation of Oral films:**

**Dose Calculation:**

- Inner radius of glass plate = 5.65 cm
- Inner Area of the plate ( r2) = 3.14×5.65 × 5.65 = 100 cm<sup>2</sup>
- No. of 9 cm<sup>2</sup> films present whole plate =100/9 =10 films. Each films contains 50 mg of drug.
- 10 films contain 500 mg drug (50 × 10).
- Labelled claim= 50 mg

**Evaluation of Ziprasidone HCl oral film:**

**Thickness:** A micrometre thread gauge can be used to measure the film's thickness. The uniformity of the film was assessed by measuring the thickness at five different sites. The thickness of the fast-dissolving film for each formulation is shown in Table 3. The thickness range for ZF1 to ZF9 batches was determined to be 0.51 mm to 0.57 mm.

**Weight variation:** The average weight of ten films is determined after a random selection of them. Weigh one film and compare it to the mean of the standard deviation. The weight variance of the ZF1 to ZF9 batch evaluations was found to range from 130.2 to 140.8 mg.

**Folding endurance:** Folding endurance of batches ZF1 to ZF9 was discovered to range from 8 to 13. Table 3 displays the folding resistance of the fast-dissolving film for all formulations.

**Percentage elongation:** It was calculated by:

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

According to an analysis of batches from ZF1 to ZF9, the percent elongation ranged between 9 and 12. Table

3 shows the % elongation of all formulations' fast-dissolving films.

**Tensile strength:** Tensile strength ratings for ZF1 through F9 batches ranged from 46.25 to 56.75 gm/cm<sup>2</sup>, according to the evaluations. The tensile strength of all formulations' fast-dissolving films is provided in Table 3.

**In-vitro disintegration using petri-dish method:** Measure the amount of time it takes for an oral film to fully dissolve in 2 ml of distilled water after adding a film to the water's surface. It was discovered that ZF1 to ZF9 batches took between 26 and 32 seconds to evaluate in-vitro. The fast-dissolving film's in vitro disintegration time for all formulations is listed in Table 3.

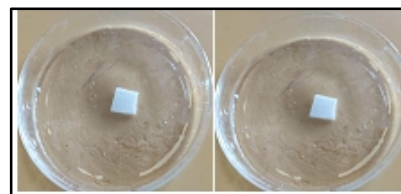


Fig. 6. Petri-dish method for in-vitro disintegration of prepared film.

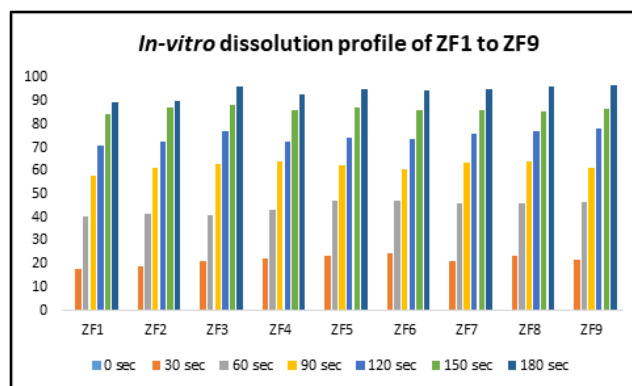
**Drug content:** A 9 cm<sup>2</sup> area film is dissolved in 50 ml of phosphate buffer 6.8 while being stirred to conduct the test. Filter the mixture through Whatman filter paper, and then re-diluent the filtrate to 100 ml in a volumetric flask using the same buffer. A UV spectrometer was used to examine the solution. According to analyses of the drug content of batches ZF1 to ZF9, it ranged from 18.96 to 20.75 mg. The outcomes are displayed in Table 3.

Table 3: Evaluation of Ziprasidone mouth dissolving film.

Formulations	Thickness (mm)	Weight vaiation (mg)	Folding Endurance	% Elongation	Tensile strength (g/cm <sup>2</sup> )	In-vitro disintegration time (sec.)	Drug content(mg)
ZF1	0.52	131.1	13	09	56.75	26	18.96
ZF2	0.51	130.2	11	11	51.45	32	19.25
ZF3	0.57	132.4	08	10	50.46	30	20.15
ZF4	0.55	134.1	11	11	49.25	28	20.42
ZF5	0.52	135.2	11	09	48.21	31	20.75
ZF6	0.56	136.4	12	10	46.25	26	19.85
ZF7	0.51	139.4	09	11	51.21	29	19.45
ZF8	0.57	140.8	11	12	52.19	28	20.25
ZF9	0.52	137.5	08	10	53.75	30	20.65

**In vitro dissolution:** Use 900 ml of phosphate buffer 6.8 and maintain it at  $37 \pm 0.5$  °C with the basket spinning at 100 rpm. Five films and a cut  $9 \text{ cm}^2$  ( $3 \times 3 \text{ cm}$ ) film sample should be placed in the basket. Every 30 seconds, take 5 ml of a sample and replace it with an

equal quantity of new Phosphate buffer 6.8. The extracted samples were filtered before being subjected to 315 nm UV spectroscopy analysis. Fig. 7 depicts information on the *in vitro* dissolution profiles of all formulations.



**Fig. 7.** *In-vitro* dissolution profile of ZF1 to ZF9.

## DISCUSSION

For the treatment of manic episodes and bipolar disorder, Ziprasidone HCl oral films were developed as part of the current project. Piperine, Citric acid, sodium saccharin, PEG 400, and HPMC E15 cps was used in batch ZF1 to ZF3. The films were translucent and clear. Additionally, consistent in thickness. The flexibility is excellent. The movies demonstrated strong mechanical qualities. The assay results show that the drug was placed correctly into the film.

Piperine, Citric acid, sodium saccharin, propylene glycol, HPMC E5, and taste were used in ZF4–ZF6. The film prepared has a nice aesthetic. The thickness is also inconsistent.

ZF3 out performed the other formulations in terms of mechanical qualities and disintegration time, taking only 30 seconds. The film's specifications were all deemed to be acceptable. The profile of dissolution was also discovered to be repeatable and desirable. The SEM morphological investigation of ZF3 reveals that it is more porous. As a result, quick medication release was made possible for fast effect.

The stability investigations took place for between one and three months. The *in-vitro* drug release, *in-vitro* disintegration, thickness, and tensile strength did not significantly change.

## CONCLUSION

The main goal of this research was to create a mouth-dissolving film using the bioenhancer piperine, Ziprasidone HCl, as well as basic components such polymers, plasticizers, sweeteners, saliva-stimulating agents, and flavours. Solvent casting was used to create the films. Piperine accelerates drug breakdown, increasing CDR by up to 99%. The HPMC E5 cps was unable to give the film thickness. HPMC E15 had good adaptability. Propylene glycol, a plasticizer, was unable to give the film flexibility and folding durability. Good folding durability, tensile strength, and % elongation was achieved using PEG 400. The improved formulation (ZF3) demonstrated

good mechanical qualities, folding durability, and mouth feel in addition to immediate drug release.

In comparison to the commercial formulation, the ZF3 demonstrated a 31-second reduction in disintegration time and 99% drug release in just three minutes.

Therefore, it was believed that the use of piperine as a natural bioenhancer, which is favourable and offers maximal drug release compared to standard dosage form, had produced quick drug release for an instant start to activity.

## FUTURE SCOPE

When used with active medications, bioenhancers can increase their pharmacological effects even when they don't have any intrinsic medicinal characteristics. As an alternative to piperine, other bioenhancers such as garlic, *Carumcarvi*, *Cuminum cyminum*, lysergol, naringin, quercetin, niaziridin, glycyrrhizin, stevia, cow urine distillate, and ginger may be used. The effects of these bioenhancers on drug release rate may be studied.

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