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Research Article

FORMULATION DEVELOPMENT AND EVALUATION OF NOVEL ORAL SOLUBLE FILMS OF ZIPRASIDONE HYDROCHLORIDE IN THE TREATMENT OF SCHIZOPHRENIA

KOTESWARI POLURI*[1], ESTHER MULPUR[1], SRINIVASA BABU PUTTUGUNTA[1], KISHORE BABU GOVADA[1]

[1]Department of Pharmaceutics, Vignan Pharmacy College, Vadlamudi, Guntur, A.P, India.

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ABSTRACT

Objective: The Present investigation deals with the formulation development and evaluation of rapid dissolving oral films of ziprasidone HCl, an atypical antipsychotic agent, belongs to class-II of BCS classification.

Methods: Ziprasidone is a poorly soluble bitter drug and hence inclusion complexes of drug with beta cyclodextrin in different compositions were prepared using kneading technique. Among the prepared compositions, the composition PM8 was chosen to incorporate the ziprasidone HCl into the films. Various film forming water soluble polymers were explored for the casting of oral soluble films. Based on their physical and mechanical properties HPMC E5 and HPMC E15 were selected for the casting of the ziprasidone HCl loaded films. The films were evaluated for various physicochemical, mechanical and thermal properties such as drug loading efficiency, disintegration time, *in vitro* drug release characters, folding endurance, tensile strength etc. X-Ray diffraction studies, Differential scanning calorimetry, Fourier transform infrared spectroscopy and stability studies were performed for the optimized formulation in order to determine the stability of the formulation and the presence of drug excipient interactions Scanning electron microscopic studies were carried out to find the morphology and the texture of the film.

Results: All the physical and mechanical properties of the films were in acceptable limits. The film F4 formulated with 20% w/v HPMC E5 showed good drug loading efficiency and 100% drug release in less than 6 min. X-Ray diffraction studies, Differential scanning calorimetry, Fourier transform infrared spectroscopy and stability studies of formulation F4 revealed the stability of the formulation. Scanning electron microscopic studies showed the morphology of the films suggesting that the films have uniform surface.

Conclusion: Overall findings suggested that ziprasidone HCl oral soluble films of HPMC E5 exhibited a desired disintegration time ≤ 50 seconds, good drug loading efficiency and stability.

Keywords: Ziprasidone HCl, Inclusion complexes, Beta cyclodextrin, Oral films, HPMC.

INTRODUCTION

Schizophrenia is a devastating disorder of the mind and brain. Anti-psychotic drugs are used for the treatment of schizophrenia. Schizophrenia is considered as most chronic, debilitating and costly illness, because it consumes a total of about $63 billion a year for direct treatment. If medication is discontinued it relapses within 2 years in about 80% of the patients. Therefore it is a treatable disease but very costly to the family and society who are affected [1]. From a layman's perspective two types of medications are used in the treatment of schizophrenia, the traditional antipsychotic medications (haldol,etc.) and the newer, atypical antipsychotic medications. According to NICE guidelines (2002) oral atypical antipsychotics are recommended as first-line treatment for patients with newly diagnosed schizophrenia[2]. Ziprasidone HCl (ZH) is a new atypical antipsychotic, proved to be effective in the treatment of schizophrenia and do not cause agranulocytosis. Chemically it is 5-[2-[4-(1, 2-benzisothiazole-3-yl)-1-piperzinyl]ethyl]-6-chloro1,3-dihydro-2H-indole-2-one. ZH is a poorly soluble drug. It is extensively metabolized after oral administration and therefore its oral bioavailability is 60%. It takes 6 to 8hrs to reach peak plasma concentration when it is administered orally. Its elimination half life is 7hrs. In a case study it is reported that inadvertent administration of intravenous ziprasidone causes bradycardia and prolongation of QT interval [3]. It is reported that oral ziprasidone administration is effective, but intramuscular ziprasidone has been shown to be more efficacious for acute agitation in individuals with schizophrenia and relatively well tolerated [4]. Though intramuscular depot injections improves treatment adherence, more predictable and stable serum concentrations of the active ingredient, it is an invasive route of drug delivery. Antipsychotics are given over a long period, because symptoms of schizophrenia such as feeling agitated and hallucinations usually go away within days but delusions disappear from three to six weeks. Therefore depot use has fallen in recent years and oral route is the more preferable route over the decades because of its non-invasive nature and patient compliance. Generally antipsychotics are administered as pills or as oral solutions. Fast dissolving oral films are more advanced form of oral solid dosage forms derived from the confection and oral care markets in the form of breath strips and became a novel and widely accepted form by consumers [5]. The oral films also combines the advantages of solid dosage forms such as stability, accuracy, content uniformity and easy swallowing, quick onset of action of liquid dosage forms. The objectives of the present study were 1.To develop formulation of ZH monohydrate orodispersible films by solvent casting technique using biocompatible and biodegradable water soluble polymers such as hydroxyl propyl methyl cellulose to enhance the ease of administration, patient compliance and oral bioavailability of ZH. 2. To evaluate the prepared films for various in vitro mechanical and physicochemical properties such as tensile strength, folding endurance, drug content, *in vitro* drug release properties using RP HPLC. 3. To carry out the stability studies of the optimized composition according to the ICH guidelines.

MATERIALS AND METHODS

Materials

Ziprasidone HCl was received as a gift sample from Jubilant life Sciences Ltd, New Delhi, India. HPMC E5 and E15 grades, Tween-80, Propylene glycol (Loba Chemicals, Mumbai, India), Beta cyclodextrin (Alkem Pharmaceutical Pvt. Ltd, Mumbai, India), Aspartame and Mannitol (Signet chemical coporation, Mumbai, India), glycerol, citric acid (Fisher scientific chemicals, Mumbai, India), Methanol (Merck Pvt. Ltd., Mumbai, India), Food flavors and colors were purchased from National scientific products (Hyderbad, India). All the ingredients used were either of analytical/HPLC grades.

Methods

RP HPLC analysis of Ziprasidone HCl

The ZH content was determined by RP HPLC method established in our laboratory (Dept.of Pharmaceutics, vignan Pharmacy College, Guntur, A.P, India) using HPLC Shimadzu equipped with a pump (Schimadzu LC-20AT prominence liquid chromatograph), Phenomenix C-18 column having 250x4.6mm, 5 µm particle and UV-

Visible detector (Schimadzu SPD-20A prominance UV/VIS detector). The mobile phase was acetonitrile : ammonium acetate buffer (pH-5) in the ratio of 80:20 with a flow rate of 1ml/min, detection at 219 nm with a retention time of 4.8 min.

Solubility studies of ziprasidone HCl in different buffers

Solubility studies of ZH were carried in water and in different phosphate buffer solutions of pH 6.4, 6.8 and 7.4 prepared as per the IP specification. To each 10ml of buffer solutions in the conical flasks excess amount of drug was added and kept on the orbital shaker at100 rpm for 2 hrs. Then the conical flasks were removed from orbital shaker and kept aside over night to equilibrate dissolved and undissloved portion of drug. On the next day samples were filtered. A volume of filtrate was taken and appropriate dilutions were made, filtered, degassed and injected in to HPLC. Using the standard calibration curve the quantity of drug dissolved was calculated.

Phase solubility studies of ziprasidone HCl with different hydrophilic polymer solutions

The above procedure was repeated to determine the solubility of ZH in different hydrophilic polymers selected for this study such as PVP, β-cyclodextrin, HEC, poloxamer, PEG8000, PEG4000 [6].

Table 1: Composition of ziprasidone HCl and β-cyclodextrin inclusion complexes

Code/name of the material	Ziprasidone Hcl (mg)	β-cyclodextrin (mg)
PM1	400	100
PM2	333.3	166.7
PM3	285.7	214.3
PM4	250	250
PM5	222.2	277.7
PM6	200	300
PM7	181.8	318.2
PM8	166.7	333.3

Preparation of Inclusion complexes of ziprasidone HCl and β-cyclodextrin

Based on solubility studies of ZH in various hydrophylic polymer solutions, cyclodextrin was selected for further study and inclusion complexes of ZH and β-cyclodextrin were prepared by kneading method. The drug and β-cyclodextrin in specified quantities were accurately weighed, transferred to a dry mortar and triturated into a wet mass by adding small quantities of water for 30min. This wet mass was dried in hot air oven at 50ºc for 1 hr. Then the dried mass was collected, pulverized, and passed through the sieve #100. These mixtures were placed in sealable covers and kept in a dessicator for further use [7]. These inclusion complexes were evaluated for drug content and *in vitro* drug release properties. Different compositions of ZH and β-cyclodextrin were endowed in table 1

Screening of the film forming polymers and the other components

Various film forming polymers such as hydroxy propyl methyl cellulose (HPMC E5, HPMC E15), Hydroxy ethyl cellulose (HEC), poly vinyl alcohol (PVA), sodium carboxy methyl cellulose (SCMC), Sodium alginate etc., were casted as films by employing solvent casting technique in order to select the suitable polymer for the preparation of ZH oral soluble films.

The required quantity (10%w/v) of polymer was accurately weighed and allowed to soak in 10 ml of water until it forms a uniform viscous solution. All other ingredients viz., propylene glycol (2.5%v/v as plasticizer), glycerine (5 %v/v humectant), coloring agent (food color q.s) and a combination of mannitol and aspartame as sweeteners in the concentration of 10 and 100 mg respectively except drug were added to the polymer solution and the mixture was sonicated for 15 min to remove any entrapped air. This solution was then casted as film on a Teflon coated plate in a measured area and allowed to dry for 2 hrs in a hot air oven at 70ºc [8]. Different film forming agents were casted into films and examined for their physical and mechanical properties such as appearance, thickness, folding endurance, and time to dissolve the film.

Preparation of ziprasidone HCl oral soluble films

Based on physical and mechanical properties of the casted placebo films, HPMC E5 and HPMC E15 were chosen for the Preparation of ZH oral soluble films. Polymer solution was prepared as described above and other components except drug were added. Then a quantity of ZH and β-cyclodextrin comlplex (PM8) equivalent to 100 mg of ZH was taken and added to the polymer solution. The entire mixture was sonicated to remove the entrapped air and to enhance the uniform dispersion of drug and cyclodextrin complex. Then the above procedure was repeated for the casting of films to obtain the drug loaded films. The compositions of the different drug loaded films were given in table II. The prepared films were wrapped in a butter paper followed by aluminium foils and kept in dessicator for further studies.

Table 2: Formulation of oral soluble films of ziprasidone HCl

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
Drug(mg)	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
HPMC E5(gm)	0.5	1	1.5	2	-	-	-	-	0.25	0.5	0.75	1	2	-	1
HPMCE15(gm)	-	-	-	-	0.5	1	1.5	2	0.25	0.5	0.75	1	-	2	1
Glycerin (ml)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Propylene glycol (ml)	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Tween-80 (%w/v)	-	-	-	-	-	-	-	-	-	-	-	-	1%	1%	1%
Aspartame (mg)	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Mannitol (mg)	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
Sodium citrate (mg)	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Preservative (mg)	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Water in ml	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10

Characterization of ziprasidone HCl oral soluble films

Mechanical Properties

Thickness

Thickness was measured using vernier calipers. The thickness was measured at five locations (one at center and four corners of the film), and the mean thickness was calculated. Samples with air bubbles, nicks and having mean thickness variation of greater than 5% are excluded from analysis.

Tensile strength

Tensile strength was measured using analog tensile tester (model TKG, FSA, India). Films free from air bubbles or physical imperfections were selected for tensile testing. The two clamps of the tensile tester were adjusted such that the distance between them is 3 cm by moving the upper clamp. During measurement, the strips were pulled by top clamp at a rate of 100mm/min; the force applied was measured until the film was broken. The film samples, which broke at the point of clamping and not between the clamps, were not

included in the calculation. Triplicate results for each film were considered. Tensile strength can be computed from the applied load at rupture as a mean of three measurements and cross sectional area of fractured film using the following equation [9].

Tensile strength (N/mm^2) = breaking force (n) /Cross sectional area of sample (mm^2)

Percentage elongation

Percentage elongation was calculated by measuring the increase in length of the film after tensile strength measurement by using the following formulae.

Percentage Elongation = $[L-L_0]$ X 100 / L_0 Where, L was the Final length, L_0 was initial length.

Folding endurance

To determine folding endurance, a strip of film was cut and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gives the value of folding endurance.

Disintegration test using slide frame method and petri dish method.

Slide frame method

The film was clamped between the frames and a drop of distilled water was placed in centre of the film with the pipette. The time required to dissolve the film and form a hole in the film was noted. Likewise this test is carried for all the films [10].

Petri dish method

In this method 2ml of water was added to a petri dish and small portion of film was taken and placed on the surface of water in the petri dish. Then the time required to completely dissolve the film was noted and the same procedure was repeated for all the films.

Drug content uniformity

A quantity of the film equivalent to 10mg of the drug was transferred into 10ml volumetric flask containing methanol. Then sonicated for 5 min to allow the drug to dissolve completely and the volume was made up with methanol. Then required dilutions were made with mobile phase to obtain a concentration of 10µg/ml of ziprasidone, filtered, degassed and injected into HPLC under above specified chromatographic conditions. Drug content was calculated from the calibration curve. Sampling was done at three different areas of the film and average of the three was considered.

Dissolution test

In vitro drug release studies were carried out in modified USP II dissolution apparatus (DS8000, Labindia). Film was placed with the help of forceps in a 100 ml glass beaker containing 20 ml of pH 6.8 phosphate buffer. The beaker was placed in a water bath of the dissolution apparatus and agitation was provided by the paddle at 100 rpm. The temperature of the dissolution media was maintained at 37 ± 0.5 °C. During the study, 2 ml of samples were withdrawn at 2, 4, 6, 8, 10, 15 and 30min and the samples were replaced by fresh buffer to maintain sink conditions [11]. The samples were diluted appropriately, filtered, degassed and injected into HPLC. The amount of drug released was calculated from the calibration curve.

Drug-excipients interaction studies

Compatibility between the drug and excipients used in the formulation is important for a dosage form to be stable. Following are the different approaches for the assessment of incompatibilities [11, 12].

- Fourier transformer infra red spectrum (FTIR)
- X-ray diffraction (X-RD)
- structural aspects were studied by SEM
- Differential scanning calorimetry (DSC)

Preparation of the sample for Fourier transform infra red spectrum (FTIR)

The samples were ground and mixed thoroughly with potassium bromide, an infrared transparent matrix, at 1:5 (Sample: KBr) ratio, respectively and the KBr discs were prepared by compressing the powders at a pressure of 5 tons for 5 min in a hydraulic press. Fourier-transform infrared (FT-IR) spectra were recorded using an FT-IR spectrophotometer (Shimadzu). Forty scans were obtained at a resolution of 4 cm^{-1}, from 4000 to 400 cm^{-1}.

Preparation of the sample for X-ray diffraction (X-RD)

Approximately 80-100 mg of sample was taken and ground to ~10 micron grain size. The NIST Si 111 was used for the routine external calibration. Sample of 5mg was loaded into glass holder and spread uniformly throughout the square glass well. Molecular arrangements of ZH and other ingredients in the films were compared by powder x-ray diffraction patterns acquired at room temperature on a Philips PW 1729 diffractometer (Eindhoven, Netherlands) using Cu Kα radiation. The data were collected over an angular range from 3° to 50° 2θ in continuous mode using a step size of 0.02° 2θ and step time of 5 seconds.

Differential Scanning Calorimetry

The differential scanning calorimetry (DSC) measurements were performed using a Shimadzu DSC-60 (Kyoto, Japan). Samples of weight approximately 5 mg were cut, sealed in aluminum pans, and analyzed in an inert atmosphere of nitrogen at flow rate of 25 ml/min. A temperature range of 0°C to 300°C was used, and the heating rate was 10°C/min.

Preparation of the sample for SEM

Films of the optimized formulation F4 were viewed using a Jeol scanning electron microscope (SEM), JSM 1600 (Tokyo, Japan) for morphological examination. Powder samples of ZH and films were mounted onto aluminum stubs using double-sided adhesive tape and then sputter coated with a thin layer of metal at 10 Torr vacuum before examination (Jeol Fine Coat, ion sputter, JFC-1100). The specimens were scanned with an electron beam of 1.2 kV acceleration potential, and images were collected in secondary electron mode.

Stability Studies

Films of formulae F4 were stored at two different storage conditions namely 30°C/60% RH and 40 °C/75% RH. Each film was wrapped in a butter paper followed by aluminium foil and placed in an aluminum pouch, which was heat-sealed at the end [12]. The films were evaluated for appearance, weight, drug content and in vitro drug release after storage for 30days, 60days and 90 days. In vitro drug release after stability studies was compared with the drug release before the stability studies to identify any change in the drug release.

RESULTS AND DISCUSSION

Solubility studies of ziprasidone HCl in water and different buffers

The salivary pH is not same for all the individuals it varies depending on the person's diet, health condition and other factors. The pH of the normal individual is in the range of pH 6.2 to 7.4. As the oral films are intended to dissolve within the oral cavity in saliva and release the drug, the solubility studies of ZH were conducted in water and in different phosphate buffers within the salivary pH range. ZH has more solubility in 6.8 pH buffer than 7.4 pH buffer and 6.4 pH buffer. The results were presented in the table 3. ZH has exhibited more solubility in 6.8 pH buffer compared to other buffers therefore phosphate buffer pH 6.8 was used as dissolution medium.

Table 3: Solubility of ziprasidone HCl in phosphate buffers with varying pH

S. No.	pH	Solubility (µg/ml) ±S.D.*
1	Water	10.06±0.01
2	6.4	24.4±0.01
3	6.8	247.2±0.03
4	7.4	169.9±0.02

S.D.*standard deviation from mean n=3

Phase solubility studies of ziprasidone in different hydrophilic polymer solutions

Phase solubility studies of ZH were carried out in different hydrophilic polymer solutions and the results were displayed in table 4. Drugs must possess some degree of aqueous solubility to be pharmacologically active, and most drugs need to be lipophilic to be able to permeate biological membranes via passive diffusion. Oral absorption of drugs with solubilities < 0.1 mg/ml is likely to be dissolution rate limited. Intensive approaches to drug development have led to an increasing number of lipophilic water-insoluble drug candidates whose clinical usefulness is hampered by their insolubility in water. These drugs are classified as Class II (i.e., poorly soluble/highly permeable) according to the Biopharmaceutics Classification System. In general, formulation techniques that increase the apparent aqueous solubility of Class II without decreasing their lipophilicity will enhance their absorption through biological membranes. ZH also belongs to BCS class-II which is poorly soluble and highly permeable drug for which solubility is the rate limiting step for its absorption and subsequently for its bioavailability.

Table 4: Solubility of ziprasidone HCl in different hydrophilic polymer solutions

S. No.	Hydrophilic polymer (1% w/v)	Solubility(µg/ml)±S.D.*
1	β-cyclodextrin	6.05±0.01
2	PVP K-30	1.67±0.02
3	PEG4000	1.27±0.01
4	PEG 8000	1.2±0.02
5	HEC	1.02±0.03
6	Poloxamer	1.00±0.01
7	Pure drug	0.875±0.04

S.D.*standard deviation from mean n=3

To select the appropriate hydrophilic polymer which enhances the solubility of ZH to a greater extent solubility studies were carried in different hydrophilic polymers and in water. The selected polymers are PVP K-30, β-cyclodextrin, PEG4000, HEC, PEG 8000, Poloxamer. Among all the hydrophilic polymers selected β-cyclodextrin enhanced the solubility of the ZH to a greater extent when compared to other selected hydrophilic polymers. This may be due to the formation of ZH and β-cyclodextrin inclusion complexes [13, 14]. The order of the hydrophilic polymers that enhanced the solubility was PVP K-30, PEG4000, PEG 8000, HEC, Poloxamer.

Preparation of Inclusion complexes of ziprasidone HCl and selection of optimum composition of drug and polymer

From the solubility studies, β cyclodextrin was chosen for the preparation of inclusion complexes of ZH and β-cyclodextrins to enhance the solubility of ZH and were prepared in different ratios. The drug content was determined using RP HPLC method as described above and was found to be 97.2±1.3% to 100.06±1.97%. The drug release profiles of the all the compositions of inclusion complexes were compared and the composition PM8 showed better drug release profile as the solubility depends on the extent of the formation of inclusion complexes which in turn proportional to the concentration of β-cyclodextrin. Therefore this composition was used for the preparation of ZH oral soluble films [15, 16].

Screening and selection of various film forming polymers

Various film forming polymers were explored for the formulation of films, evaluated for various Physical and mechanical properties. Films were formulated using solvent casting technique on Teflon coated plate and the films were uniform and easily peelable [11]. Formulations containing 1%, 2% and up to 5% w/v solutions of different polymers could not yield films or the films were very thin and hence screening of films was done with 10%w/v solutions. The disintegration time of HPMC E5 and E15 was found to be less than 50 seconds these two polymers were selected and used for further study. All the results were given in the table 5.

Table 5: Physical and mechanical properties of various film forming polymers

Polymer	Appearance	Folding endurance ±S.D.*	Thickness in mm ± S,D.*	Disintegration time (sec) ±S.D.*
HPMCE5	Transparent	53±1.2	0.1±0.2	24±2.2
HPMCE15	Transparent	65±2.3	0.16±0.1	43±3.1
HEC	Transparent	74±1.7	0.19±0.2	55±1.2
PVA	Transparent	120±1.9	0.2±1.2	300±2.3
SCMC	Transparent	35±2.1	0.21±0.11	300±2.5
Sodium alginate	Transparent	46±1.5	0.23±0.13	49±1.7
Guar gum	Transparent	53±2.2	0.21±0.10	52±2.2
Xanthan gum	Transparent	42±1.1	0.20±0.22	69±2.5

S.D.*standard deviation from mean n=3

Preparation and Characterization of drug loaded films

From the dissolution profiles of ZH and β-cyclodextrin inclusion complexes and initial screening studies of film forming polymers, it was conferred that the composition PM8 and HPMC E5 and HPMC E15 were suitable for the preparation of oral fast dissolving films containing ZH. Therefore composition PM8 was incorporated into the polymer solution and films were casted. Effects of formulation variables such as the concentration and type of polymer on various physicochemical and mechanical properties were also studied.

Mechanical properties

Thickness, tensile strength, percent elongation, elastic modulus and Folding Endurance

Thickness of the films increased as the percent weight of the film forming polymer was increased [17]. Not only the percent of the film forming agents determines the thickness but the viscosity grade of the film forming agent also influences thickness of the films. The films formulated with HPMC E15 grade were thicker than the films of the HPMCE5 and the thickness of the films formulated with combination of HPMCE5 and HPMCE15 have intermediate thicknesses compared to their individual films.

Tensile strength is defined as the maximum stress applied at a point at which the film specimen breaks. The tensile strength of the film is important to resist the mechanical movements that occur during the packing, storage and shipping of the films. Depending on the type and viscosity grade of film former the tensile strength varied and high tensile strength was observed in films prepared with HPMCE15 than E5 grade [18]. Tensile strength and elongation are also significantly influenced by the type and percent of plasticizer present. Films without plasticizer were brittle in nature and had tendency to break during peeling. The films prepared with high concentration of plasticizer resulted in sticky and distorted films. Glycerin and Propylene glycol are commonly added to all the formulations. To the formulations F13, F14, F15 1% tween 80 is added in addition to glycerin and propylene glycol. The films of F13, F14, F15 were more smooth and they have high tensile strength and Percent elongation compared with films of other formulations. The folding endurance was highest for the films F12 (113±0.2) and lowest for F 9 (55±0.3). All the mechanical properties of the films are within the required range and the results were given in table 6.

Table 6: Mechanical properties of drug loaded films

S. No.	Formulation	Thickness (mm) ±S.D.*	Tensile Strength (MPa) ±S.D.*	Percent Elongation ±S.D.*	Elastic Modulus ±S.D.*	Folding endurance ±S.D.*
1	F1	0.1±0.01	1.82±0.1	75.23±2.34	1.98±0.057	56±0.1
2	F2	0.16±0.03	2.21±0.2	63.69±1.64	3.03±0.18	65±0.4
3	F3	0.19±0.02	2.34±0.3	49.57±4.56	2.67±3.38	78±0.3
4	F4	0.23±0.01	2.54±0.2	56.71±1.59	1.75±1.58	92±0.5
5	F5	0.12±0.04	1.90±0.1	71.50±5.02	2.79±0.14	55±0.1
6	F6	0.16±0.03	2.36±0.2	59.57±4.09	1.72±0.26	76±0.3
7	F7	0.18±0.02	2.67±0.1	67.95±3.61	1.40±0.33	87±0.1
8	F8	0.25±0.01	2.93±0.2	62.23±2.34	2.74±1.71	107±0.2
9	F9	0.1±0.04	2.03±0.3	69.27±3.46	3.69±0.34	55±0.3
10	F10	0.15±0.01	2.53±0.2	42.13±6.87	2.73±2.62	68±0.2
11	F11	0.19±0.03	2.94±0.2	59.57±2.99	2.51±3.14	80±0.1
12	F12	0.26±0.02	3.25±0.1	62.23±4.41	3.28±1.87	113±0.2
13	F13	0.23±0.01	2.10±0.2	89.98±2.12	2.45±1.24	92±0.3
14	F14	0.25±0.05	2.52±0.3	93.05±3.56	1.22±3.64	102±0.2
15	F15	0.26±0.03	2.95±0.2	94.12±5.72	2.30±0.34	105±0.1

S.D.*standard deviation from mean n=3

Disintegration time

Disintegration test for the films was carried out by employing petri plate technique and slide frame technique. The results were given in the table 7. As the fast dissolving films are intended to dissolve in less than a minute there does not exists a clear difference between the disintegration time and dissolution both are indistinguishable because in case of fast dissolving films during disintegration time the total amount of drug is released [10]. All the formulations were disintegrated in less than 75 seconds and among all the films the films formulated with HPMC E5 exhibited less disintegration time and this may be due to its low viscosity. The disintegration time was further reduced with the addition of tween 80 to the formulation and rep.resented by F13, F14 and F15 and the results were given in table 7.

Drug loading efficiency

The percent drug loading efficiency of all the formulations is in the range from 80.30±0.2% to 101.2±0.6%. The drug loading efficiency was increased with increasing concentration of polymer. There is no significant increase or decrease in the percent drug loading efficiency due to the addition of tween-80 in the formulations F13, F14 and F15. The data was given in table 7.

Table 7: *In vitro* disintegration time and percent drug loading efficiency of prepared films

S. No.	Formulation Code	D.T of films using Petri plate method (seconds) ±S.D.*	D.T of films using Slide frame method (seconds) ±S.D.*	Percent drug loading Efficiency ±S.D.*
1	F1	26±0.1	30±0.2	80.30±0.2
2	F2	42±0.7	45±0.3	82.32±0.3
3	F3	53±0.3	55±0.5	87.72±0.5
4	F4	45±0.5	50±0.2	101.2±0.6
5	F5	30±0.2	33±0.5	81.72±0.2
6	F6	48±0.1	52±0.3	83.47±0.7
7	F7	59±0.2	61±0.6	89.08±0.5
8	F8	67±0.6	71±0.5	95.51±0.6
9	F9	32±0.3	35±0.1	82.96±0.2
10	F10	54±0.5	58±0.2	83.93±0.3
11	F11	61±0.1	65±0.7	87.24±0.5
12	F12	70±0.2	72±0.2	90.53±0.1
13	F13	52±0.4	55±0.3	98.65±0.2
14	F14	64±0.2	67±0.6	97.12±0.1
15	F15	67±0.1	71±0.2	91.92±0.6

S.D.*standard deviation from mean n=3

***In vitro* drug release studies**

As the drug loading efficiency is more with F4, F8, F12 and F13, *in vitro* drug release studies were carried out with these formulations. The cumulative percent drug released was 100.04±4.1, with in 6 min in case of F4 and from 97.89±7.7 to 99.89±2.6 after 8 min in case of F8, F12 and F13. *In vitro* drug release profiles of the films were compared with pure drug and marketed capsules. Only 5% of drug was released within 6min for the pure drug and 15% of drug was released for the marketed capsules.

Drug excipient incompatibility studies

FTIR

Transmission infrared spectra of ZH, and films were acquired to draw information on any incompatibility in the formulation. The IR report of pure ZH and the F4 film was given in the fig 1A and 1B.

In the infrared spectrum, pure ZH exhibited a broad peak at 3414 cm^{-1}, which is assigned to the N-H of the amine, while a peak at 3196 cm^{-1} is that of N-H bond of amide, Further, in the C-H stretch region of FTIR spectrum, the higher intensity peak at 2932 cm^{-1} is assigned to the asymmetric modes of CH2. In addition, the characteristic band due to CH2 for the alkanes which usually occurs at 2932 cm^{-1} was also present in the sample. An amide bond peak was present in the spectra and the C=O stretch of amide bond was observed at 1751cm^{-1}. The high intensity peak at 1631cm^{-1} represents the alkene –C=C- bonds. The peak at 1560 cm^{-1} represents N-O bond of the amide group. The sharp peaks at 1493cm^{-1} and 1473cm^{-1} indicates the presence of –C=C- alkene bonds of the aromatic ring. The peaks at 1290 cm^{-1} and 1242 cm^{-1} were assigned to strong N-H bending vibrations of secondary amines. The sharp high intense peaks at 773cm^{-1} and 743cm^{-1} represents the –C-Cl- bond of Alkyl halide functional group. The peaks at972 cm^{-1}, 947cm^{-1}, 835cm^{-1} indicates

the presence of =C-H bond of the alkene group. In comparison to the pure drug, the spectrum of the film was not sharp. The presence of residual moisture content and glycerol in films resulted in a broad peak and the peak representing –N-H- bond of the amine group was shifted to 3360cm^{-1}. The peak at 2934 cm^{-1} is a representative of O-H stretch bond in the film, the peak at 2932cm^{-1}, the peak at 2932cm^{-1} was shifted to 2885cm^{-1} which is a representative of –C-H- bond of alkane. The peak at 1639cm^{-1} represents the amide group. Peak at 1421cm^{-1} is an indication of the presence of –C-H- bond of the alkane group. The peak representing aromatic -C=C- group was shifted from 1493cm^{-1} to 1460cm^{-1}. The peak at 1338cm^{-1} and 1203cm^{-1} represents –C-N- bond of amine group, the peaks from 947cm^{-1} to 852cm^{-1} represents –C=C- bond of alkene. The peak represents 652cm^{-1} to 574cm^{-1} represents –C-Cl.

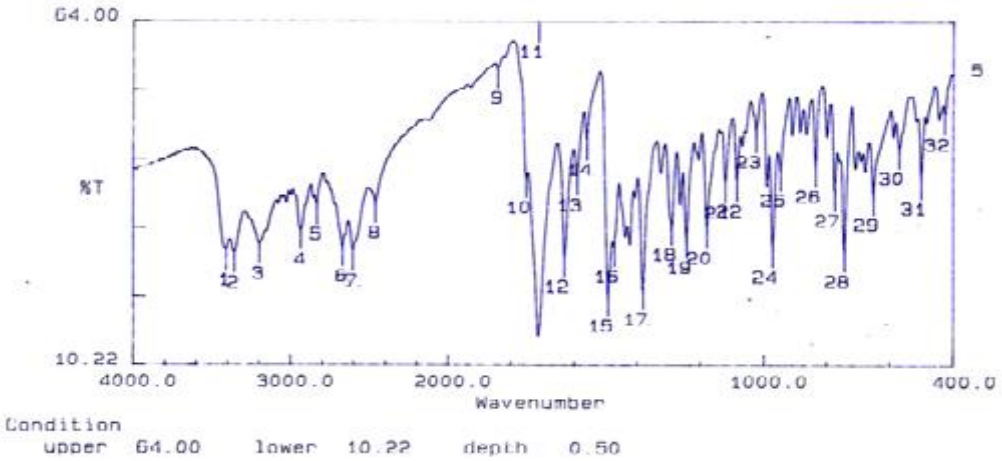

Fig 1A: IR Spectrum of pure drug ziprasidone HCl

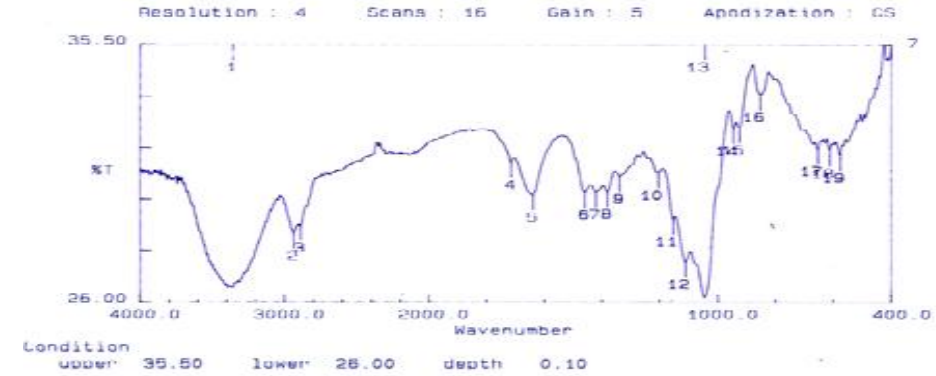

Fig 1B: IR Spectrum of F4 formulation

DSC Thermogram of the F4 Film

The DSC thermograms of pure ZH and F4 films were shown in Fig 2A and 2B.

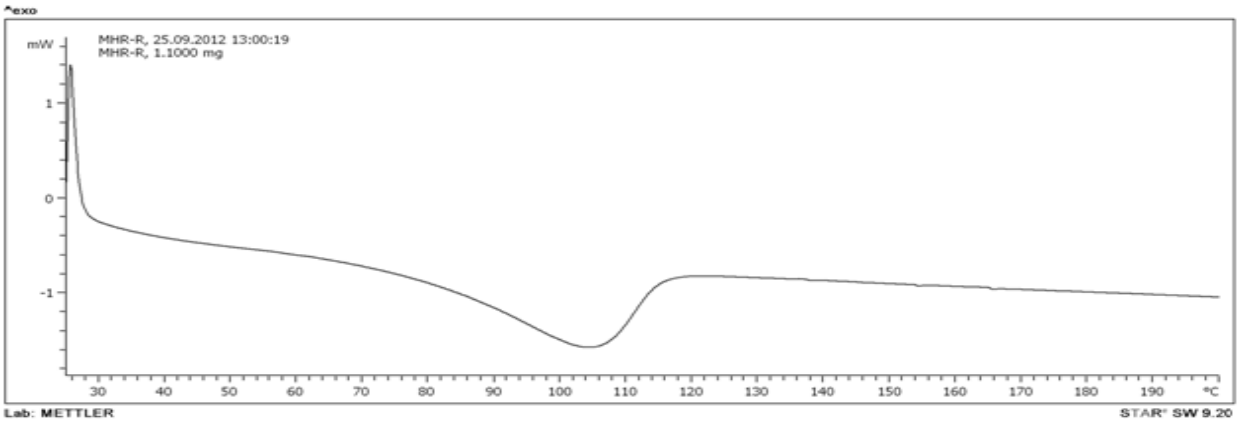

Fig 2A: DSC Themogram of ziprasidone HCl

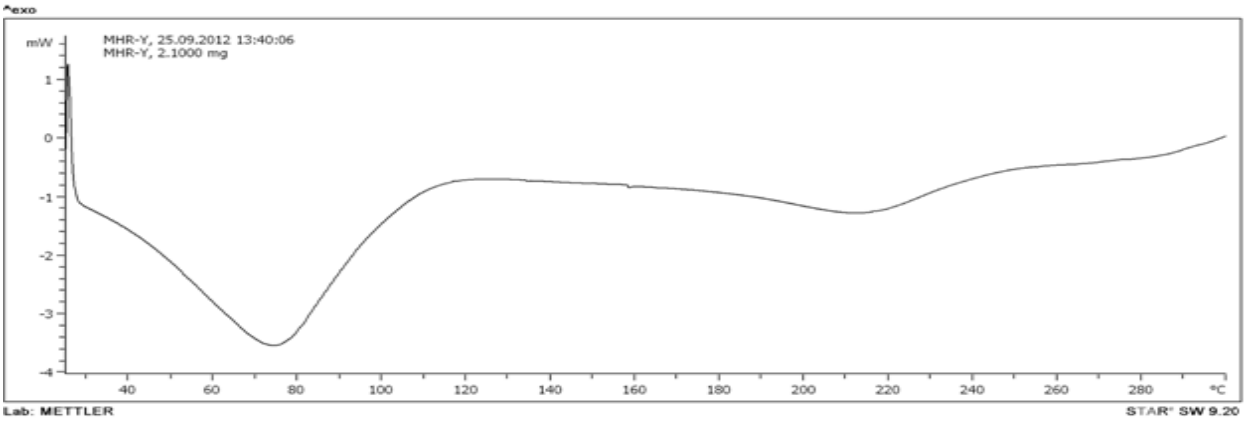

Fig 2B: DSC Thermogram of F4 formulation

The melting endotherm was observed at 105°C for pure ziprasidone and that of the film F4 melting endotherm was shifted towards left side of thermogram. This is because of conversion of the ZH to its amorphous form during the process of complexation with the betacyclodextrins and during the casting of film. The results suggested that the crystalline drug has been transformed to the amorphous form [19].

X-ray Diffraction Studies

X-ray diffraction pattern of pure drug ZH and ZH film were obtained and compared, which revealed marked differences in the molecular state of ZH. The ZH in the diffractogram exhibited high intensity peaks at the following 2θ values: 11.2°, 14.1°, 15.4°, 17.9°,22.4°, 24.2° and 25.3°. Among these, the peak of highest intensity was located at 24.2° 2θ, and all were sharp peaks indicating the more crystalline nature of the pure form. When the diffraction pattern of ziprasidone in the film was compared with that of pure ziprasidone, the pattern differed to a large extent. All the high intensity peaks in the ziprasidone have shown a characteristic broad hump in the film diffractogram this halo diffraction pattern (broad hump) is an indication of the predominantly amorphous form of ziprasidone in films. The X-RD diffractogram of the pure ZH was given in the fig 3A and the X-RD diffractogram was given in the fig 3B.

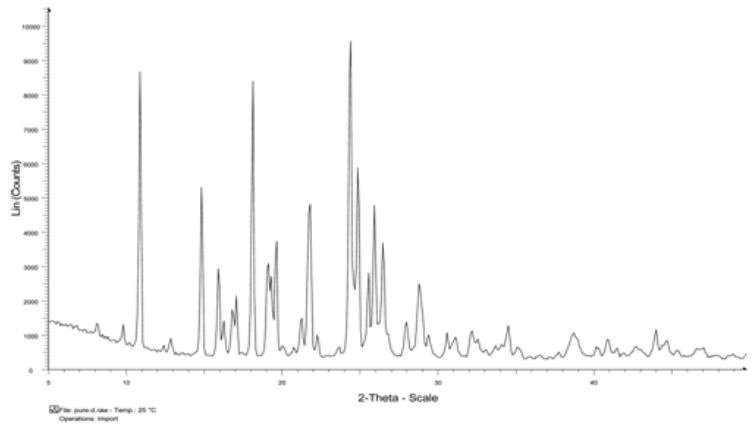

Fig 3A: X-Ray diffractogram of ziprasidone HCl

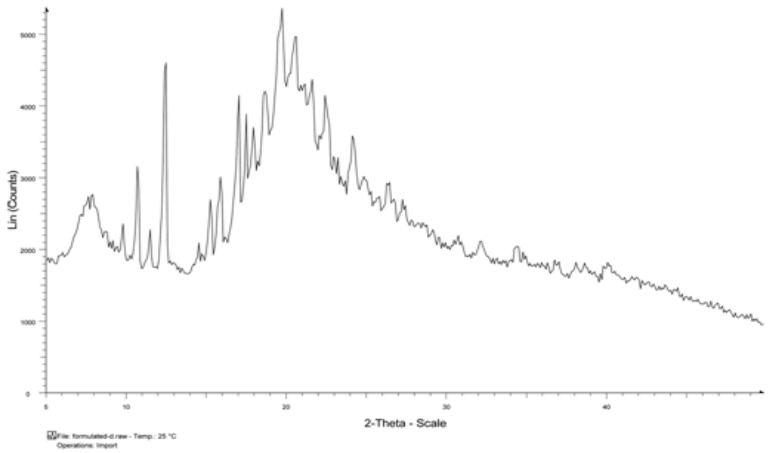

Fig 3B: X-Ray diffractogram of F4 formulation

Structural Aspects of the film using Scanninng electron microscopy

SEM photomicrographs of control film of F4 (containing no ZH) and ZH F4 films were acquired and compared. The morphology of control film was plain and the picture appeared dark, indicating that the control film has a smooth surface. In contrast to control film, the typical surface appearance of the films suggests that ZH is not only dispersed uniformly in the film matrix but also projected onto the surface of film. The appearance is same at different areas of the films suggesting that the films are uniform [20]. The SEM photographs of the control film and F4 formulation were given in fig 4A and 4B.

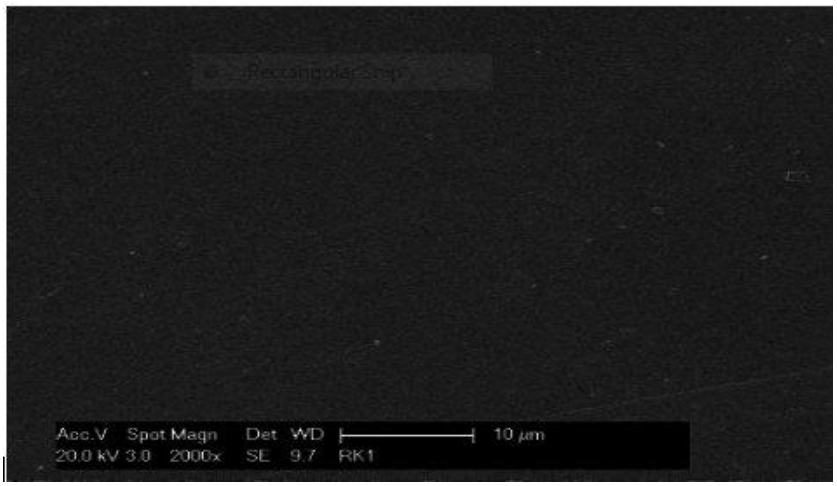

Fig. 4A: Scanning electron micrograph of Placebo film (F4 formulation)

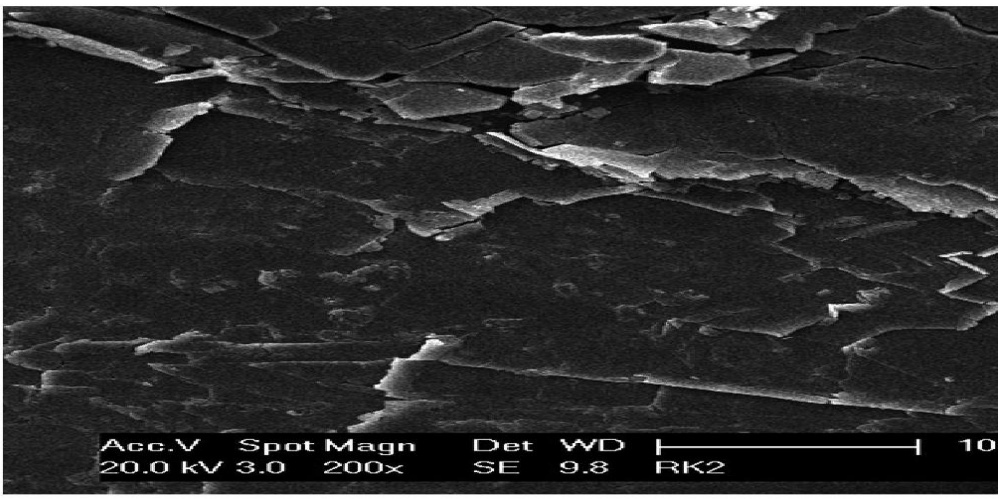

Fig. 4B: Scanning electron micrograph of F4 formulation

Stability studies

The films did not show any significant change in appearance, weight loss and ZH content on storage. The *in vitro* dissolution profiles were almost same as that of the dissolution profiles before the storage which indicated that F4 films were stable after storage. The data was given in table 8.

Table 8: Stability Studies of the F4 Formulation

S. No.	Time period (days)	Storage conditions	Percent drug content (w/v) ±S.D.*
1	0		99.78±3.85
2	30	30°C and 60% RH	98.43±3.27
3	30	40°C and 75% RH	99.06±4.58
4	90	30°C and 60% RH	98.33±4.69
5	90	40°C and 75% RH	98.44±4.51

S.D.*standard deviation from mean n=3

CONCLUSION

Solubility of ZH was enhanced by preparing inclusion complexes with β-cyclodextrin in 1:2 ratio using kneading technique. Oral dissolving films were formulated with HPMC E5 and E15 by employing solvent casting technique. The inclusion complexes were successfully incorporated into the films. All the films were evaluated for physicochemical properties such as thickness, tensile strength, percent elongation, folding endurance, drug loading efficiency, disintegration time and in vitro drug release characteristics. Films prepared with 20%w/v of HPMC E5 showed 101.2% drug loading efficiency, disintegration time less than 45 sec and 100% of drug release within 6 minutes in *in vitro* dissolution studies. Drug-excipient incompatibility studies were conducted using FTIR, X ray diffraction, DSC and SEM. These studies revealed the compatibility between the drug-excipients of the film. Stability studies were also carried out for the optimized formulation for three months under two different conditions 30 °C and 60% RH, 40 °C and 75% RH. The films were stable throughout the stabilities studies.

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