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

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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, belong 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/w 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. Antipsychotic 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 $563 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 (haldoLeteL) 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-[(2, 2-benzisothiazole-3-yl)-1-piperazine]ethyl]-6-chloroL3-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 bio compatible 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 (Pisher scientific chemicals, Mumbai, India), Methanol (Merck Pvt. Ltd., Mumbai, India), Food flavors and colors were purchased from National scientific products (Hyderabad, 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, vigan Pharmacy College, Guntur, A.P, India) using HPLC Shimadzu equipped with a pump (Shimadzu LC-20AT prominence liquid chromatograph), Phenomenex C-18 column having 250x4.6mm, 5 μm particle and UV-
Visible detector (Shimadzu SP-20A prominence 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 at 100 rpm for 2 hrs. Then the conical flasks were removed from orbital shaker and kept aside overnight to equilibrate dissolved and undissolved 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**

<table>
<thead>
<tr>
<th>Code/name of the material</th>
<th>Ziprasidone HCl (mg)</th>
<th>β-cyclodextrin (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PM1</td>
<td>400</td>
<td>100</td>
</tr>
<tr>
<td>PM2</td>
<td>333.3</td>
<td>166.7</td>
</tr>
<tr>
<td>PM3</td>
<td>285.7</td>
<td>214.3</td>
</tr>
<tr>
<td>PM4</td>
<td>250</td>
<td>250</td>
</tr>
<tr>
<td>PM5</td>
<td>222.2</td>
<td>277.7</td>
</tr>
<tr>
<td>PM6</td>
<td>200</td>
<td>300</td>
</tr>
<tr>
<td>PM7</td>
<td>181.8</td>
<td>318.2</td>
</tr>
<tr>
<td>PM8</td>
<td>166.7</td>
<td>333.3</td>
</tr>
</tbody>
</table>

**Preparation of Inclusion complexes of ziprasidone HCl and β-cyclodextrin**

Based on solubility studies of ZH in various hydrophilic 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 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 complex (PMB) 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**

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
<th>F9</th>
<th>F10</th>
<th>F11</th>
<th>F12</th>
<th>F13</th>
<th>F14</th>
<th>F15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug (mg)</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
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<tr>
<td>HPMC E5 (gm)</td>
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<td>1</td>
<td>1.5</td>
<td>2</td>
<td>-</td>
<td>-</td>
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<tr>
<td>HPMC E15 (gm)</td>
<td>-</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
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<td>0.5</td>
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<tr>
<td>Glycerin (ml)</td>
<td>0.25</td>
<td>0.25</td>
<td>0.25</td>
<td>0.25</td>
<td>0.25</td>
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<td>0.25</td>
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<tr>
<td>Tween-80 (%v/v)</td>
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<td>-</td>
</tr>
<tr>
<td>Aspartame (mg)</td>
<td>10</td>
<td>10</td>
<td>10</td>
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<td>10</td>
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<tr>
<td>Mannitol (mg)</td>
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<td>100</td>
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<td>100</td>
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<td>100</td>
<td>100</td>
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<td>100</td>
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<tr>
<td>Sodium citrate (mg)</td>
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<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
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<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
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<tr>
<td>Preservative (mg)</td>
<td>0.05</td>
<td>0.05</td>
<td>0.05</td>
<td>0.05</td>
<td>0.05</td>
<td>0.05</td>
<td>0.05</td>
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<td>0.05</td>
<td>0.05</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>Water in ml</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
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<td>10</td>
</tr>
</tbody>
</table>

**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 is recorded. The strips broke at the point of clamping and not between the clamps, were not pulled by top clamp at a rate of 100mm/min; the force applied is recorded.
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 (Joel 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 completely within the oral cavity in saliva and release the drug, the solubility studies of ZH were conducted in phosphate buffers pH 6.8 and 7.4. Each film was wrapped in a butter paper followed by aluminium foil and placed in an aluminium 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 30 days, 60 days 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.

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

<table>
<thead>
<tr>
<th>S. No.</th>
<th>pH</th>
<th>Solubility [µg/ml] ± S.D.*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6.2</td>
<td>10.0±0.01</td>
</tr>
<tr>
<td>2</td>
<td>6.4</td>
<td>24.4±0.01</td>
</tr>
<tr>
<td>3</td>
<td>6.8</td>
<td>247.2±0.03</td>
</tr>
<tr>
<td>4</td>
<td>7.4</td>
<td>169.9±0.02</td>
</tr>
</tbody>
</table>

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**

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Hydrophilic polymer (1%)</th>
<th>Solubility(μg/ml)±S.D.*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>β-cycloedextrin 2%</td>
<td>0.05±0.01</td>
</tr>
<tr>
<td>2</td>
<td>PVP K-30</td>
<td>1.67±0.02</td>
</tr>
<tr>
<td>3</td>
<td>PEG 4000</td>
<td>1.27±0.01</td>
</tr>
<tr>
<td>4</td>
<td>PEG 8000</td>
<td>1.2±0.01</td>
</tr>
<tr>
<td>5</td>
<td>HEC</td>
<td>1.02±0.03</td>
</tr>
<tr>
<td>6</td>
<td>Poloxamer</td>
<td>1.00±0.01</td>
</tr>
<tr>
<td>7</td>
<td>Pure drug</td>
<td>0.87±0.04</td>
</tr>
</tbody>
</table>

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-cycloedextrin, PEG4000, HEC, PEG 8000, Poloxamer. Among all the hydrophilic polymers selected β-cycloedextrin 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-cycloedextrin 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-cycloedextrin 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 100.0±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 pealable [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 Table 5.

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

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

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

Preparation and Characterization of drug loaded films

From the dissolution profiles of ZH and β-cycloedextrin 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 HPMC E15 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 F9 (55±0.3). All the mechanical properties of the films are within the required range and the results were given in Table 6.
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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 3360 cm⁻¹. The peak at 2934 cm⁻¹ is a representative of O-H stretch bond in the film, the peak at 2932 cm⁻¹ was shifted to 2885 cm⁻¹ which is a representative of -C-H bond of alkane. The peak at 1639 cm⁻¹ represents the amide group. Peak at 1421 cm⁻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 1493 cm⁻¹ to 1460 cm⁻¹. The peak at 1338 cm⁻¹ and 1203 cm⁻¹ represents -C-N- bond of amine group, the peaks from 947 cm⁻¹ to 852 cm⁻¹ represents -C=C- bond of alkene. The peak represents 652 cm⁻¹ to 574 cm⁻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 Thermogram of ziprasidone HCl**
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 betacycloceltrins 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.
Structural Aspects of the film using Scanning 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.

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

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Time period (days)</th>
<th>Storage conditions</th>
<th>Percent drug content (w/v) ± S.D.*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>30°C and 60% RH</td>
<td>99.78 ± 3.85</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>40°C and 75% RH</td>
<td>98.43 ± 3.27</td>
</tr>
<tr>
<td>3</td>
<td>90</td>
<td>30°C and 60% RH</td>
<td>99.06 ± 4.58</td>
</tr>
<tr>
<td>4</td>
<td>90</td>
<td>40°C and 75% RH</td>
<td>98.33 ± 4.09</td>
</tr>
</tbody>
</table>

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 stability studies.

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