3.1 Aim of the present work

Recently rapidly dissolving dosage forms (RDDF) have started gaining popularity and acceptance as new drug delivery systems due to their unique properties (1,2). They quickly disintegrate and dissolve in the mouth and can be administered without water, making them particularly suitable for paediatric and geriatric patients. RDDF include tablets, films and microspheres. Tablets are the most commonly used amongst them.

Orally disintegrating drug delivery systems were originally devised by scientists at Wyeth Laboratories in the UK during the 1970s and their research lead to the outcome of Zydis, a patented formulation technology. RDDF are referred by different names like fast dissolving, porous tablet, melt-in-mouth, oro-dispersible, quick dissolving, orally disintegrating or rapidly disintegrating dosage forms (1,3,4). The commonly available patented formulations are freeze dried type of dosage forms, which possess better convenience for use, enhanced bioavailability, and higher stability of the dosage form (3-5).

Advantages of RDDF include:

- Ease of administration for patients who are mentally ill, disabled and uncooperative
- Requires no water uptake
- Quick disintegration and dissolution
- Leaves minimal or no residue in the mouth after administration

The aim of the present investigation was to develop rapidly dissolving dosage forms of the film type. Rapidly dissolving films (RDF) have already gained popularity in the form of breath freshener as products available from Warner Lambert and Wrigley's in the US and Europe, and Boots in the UK, as well as for vitamin products (2,5-8). Zengen recently launched a chloraseptic relief strip in the US for therapeutic purposes to deliver benzocaine, for treatment of sore throats (8). The film is to be simply placed on a patient's tongue or any oral mucosal tissue where due to instant wetting by saliva, the film rapidly hydrates and may adhere onto the site of application. It then rapidly disintegrates and dissolves to release the medicament. It might have mucosal absorption
Aim of the present work

or, if not adhered to the mucosa, allows oral gastrointestinal absorption with quick-dissolving property (8).

**The advantages of RDF are:**
- faster absorption
- improved portability
- ease of administration
- accurate dosing
- cost-effectiveness
- improved patient compliance
- provide larger surface area for mucosal absorption

Suitable drug candidates for RDF include nicotine replacement transdermal delivery (NRTD), anti-ulcer and antihistamine drugs. Antipsychotic and sleeping disorder drugs are also potential candidates for prescription products.

**Important considerations when developing RDFs include:**
- Drug loading which is a major concern for RDF. It leads to increased film thickness which can alter the characteristics of the RDF making it a slowly disintegrating one.
- Overcoming the unwanted taste of certain API can also be a challenge to the formulator.
- Dry storage conditions are essential to maintain stability, as RDF are highly sensitive to temperature and humidity.
- Patients ingesting films of an API must be cautioned about the side-effects it is likely to produce instantaneously because of the rapid action of these dosage forms. e.g. Diphenylhydramine causing drowsiness effects. The patient may easily carry the medication at all the times so he/she should be warned against taking the films beyond normal recommended dosage schedules (7,9).

The RDF is preferably formulated using the solvent-casting method, whereby the water-soluble ingredients are dissolved to form a clear viscous solution (2). The API and other agents are dissolved in smaller amounts of the solution, and combined with the bulk. This mixture is then added to the aqueous viscous solution. The entrapped air is removed by vacuum. The resulting solution is casted as a film and allowed to dry, which is then cut.
into pieces of the desired size. Water-soluble hydrocolloids used to prepare RDF include hydroxypropyl methyl cellulose (HPMC), hydroxypropyl cellulose (HPC), pullulan, sodium alginate, pectin and carboxymethyl cellulose (CMC) (9). Another method used for the formulation of RDF is hot melt extrusion technique (HME). This is commonly used to prepare granules, sustained-release tablets, transdermal and transmucosal drug delivery systems. Processing films by this technique, involves shaping a polymer into a film via the heating process rather than through the traditional solvent casting method (9).

The purpose of the present investigation was to formulate and develop RDF for oral use and deliver maximum amount of the drug in shortest duration of time with most comfort to the patient. Cetirizine, an anti-histaminic drug was used in the present investigation. Manufacturing of RDF was carried out by solvent casting method. As cetirizine hydrochloride has bitter taste, taste masking techniques used in the study include addition of sweeteners and flavours, use of cyclodextrin and derivatives and ion-exchange resin. Various film forming polymers like HPMC E LV grades, HPC LF and pullulan were used in the formulation of rapidly dissolving films. Evaluation of the RDF was done by taste masking, in-vitro, in-vivo disintegration and in-vitro dissolution study. Other parameters measured for evaluation of RDF include mechanical properties like tensile strength, % elongation and elastic modulus study. Techniques like Scanning electron microscopy (SEM), Fourier transfer electron microscopy (FTIR), Differential electron microscopy (DSC) and X ray diffractometry (XRD) were also used for the characterization of the films wherever necessary.
3.2 Identification and Estimation of Cetirizine hydrochloride

3.2.1 Identification of Cetirizine hydrochloride

A. Determination by infra red absorption spectrophotometry.

The spectrum of the sample was compared with reference spectrum of cetirizine hydrochloride as shown in Figure 1.

Figure 1
FTIR spectra of Cetirizine hydrochloride sample and reference
Aim of the present work

The FTIR spectra of the pure drug showed significant band at 3427, 2839, 2587, 1741 and 1600 cm\(^{-1}\) which indicates the presence of hydroxyl, ether stretching, tertiary amine salt, carbonyl groups and phenyl nucleus skeletal stretching respectively which confirms the purity of the drug. The FTIR of the sample was compared with the reference as shown in Indian Pharmacopoeia, 2007.

B. Determination by Ultraviolet spectroscopy

20 mg of cetirizine hydrochloride was dissolved in 50 ml of 1.03% w/v solution of hydrochloric acid and diluted to 100 ml with the same acid.10 ml of this solution was diluted to 100 ml with the acid. When examined in the range 210 to 350 nm, the resulting solution showed an absorption maximum at 231 nm. The specific absorbance at 231 nm was 361(359 to 381).
3.2.2 Estimation of Cetirizine hydrochloride

**Standard curve of Cetirizine hydrochloride in different dissolution medium**

In the present study, Cetirizine hydrochloride was estimated by UV-visible spectroscopy method in three dissolution medium namely distilled water, 0.1 N HCl and simulated saliva.

3.2.2.1 Standard curve in distilled water

**Preparation of standard curve in distilled water**

100 mg cetirizine hydrochloride was accurately weighed and dissolved in distilled water to 100 ml. 10 ml of the solution was taken from the stock and further diluted with distilled water to make 100 ml. This solution was further diluted to obtain concentrations in the range of 5-30 µg / ml. The diluted solutions were scanned using Shimadzu double beam UV-visible spectrophotometer from wavelength 200-400 nm range. Absorption maximum ($\lambda_{\text{max}}$) was obtained at 231 nm (Figure 2). A standard curve was plotted to study the linearity of Beer Lambert’s law (Figure 3).

Figure 2
UV spectra of cetirizine hydrochloride in distilled water
Aim of the present work

Table 1

**Standard curve in distilled water**

<table>
<thead>
<tr>
<th>Concentration (µg/ml)</th>
<th>Absorbance (A)</th>
<th>Absorbance (B)</th>
<th>Absorbance (C)</th>
<th>Average Absorbance</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>0.132</td>
<td>0.155</td>
<td>0.15</td>
<td>0.146</td>
</tr>
<tr>
<td>8</td>
<td>0.213</td>
<td>0.223</td>
<td>0.236</td>
<td>0.224</td>
</tr>
<tr>
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<td>0.296</td>
<td>0.290</td>
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<tr>
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<td>0.344</td>
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</tr>
<tr>
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<td>0.446</td>
<td>0.443</td>
<td>0.438</td>
</tr>
<tr>
<td>20</td>
<td>0.565</td>
<td>0.576</td>
<td>0.59</td>
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<tr>
<td>30</td>
<td>0.867</td>
<td>0.869</td>
<td>0.869</td>
<td>0.868</td>
</tr>
</tbody>
</table>

Figure 3

Standard curve of cetirizine hydrochloride in distilled water

Result of regression statistics

R Square 0.99925
Intercept -0.00166
X Variable 0.029015
Aim of the present work

Equation of the line
Absorbance = Slope X Concentration + Intercept
Absorbance = 0.029 Concentration -0.00166
Linearity was observed between 5 to 30 µg / ml.

3.2.2.2 Standard curve in 0.1N HCl

Preparation of standard curve in 0.1 N HCl
100 mg cetirizine hydrochloride was accurately weighed and dissolved in 0.1 N HCl to 100 ml. 10 ml of the solution was taken from the stock and further diluted with 0.1N HCl to make 100 ml. This solution was further diluted to obtain concentrations in the range of 5-25 µg / ml. The diluted solutions were scanned using Shimadzu double beam UV-visible spectrophotometer from wavelength 200-400 nm range. Absorption maximum ($\lambda_{max}$) was obtained at 231 nm (Figure 4). A standard curve was plotted to study the linearity of Beer Lambert’s law (Figure 5).

Figure 4
UV spectra of cetirizine hydrochloride in 0.1 N HCl
Aim of the present work

Table 2

Standard curve in 0.1 N HCl

<table>
<thead>
<tr>
<th>Concentration (µg/ml)</th>
<th>Absorbance</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(A)</td>
<td>(B)</td>
<td>(C)</td>
<td>Average Absorbance</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
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<td>0.168</td>
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<td>0.185</td>
</tr>
<tr>
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<td>0.293</td>
<td>0.28</td>
<td>0.327</td>
<td>0.3</td>
</tr>
<tr>
<td>10</td>
<td>0.392</td>
<td>0.344</td>
<td>0.381</td>
<td>0.372</td>
</tr>
<tr>
<td>12</td>
<td>0.443</td>
<td>0.396</td>
<td>0.444</td>
<td>0.428</td>
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<tr>
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<td>0.515</td>
<td>0.561</td>
<td>0.545</td>
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<tr>
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<td>0.679</td>
<td>0.741</td>
<td>0.714</td>
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<tr>
<td>25</td>
<td>0.919</td>
<td>0.86</td>
<td>0.92</td>
<td>0.900</td>
</tr>
</tbody>
</table>

Figure 5

Standard curve of cetirizine hydrochloride in 0.1 N HCl

Result of regression statistics

R Square 0.999728
Aim of the present work

Intercept 0.01164
X Variable 0.035395
Equation of the line
Absorbance = Slope X Concentration + Intercept
Absorbance= 0.0354Concentration +0.01164
Linearity was observed between 5 to 25 µg / ml.

3.2.2.3 Standard curve in simulated saliva

Preparation of standard curve in simulated saliva
100 mg cetirizine hydrochloride was accurately weighed and dissolved in simulated saliva to 100 ml. 10 ml of the solution was further diluted with simulated saliva to 100 ml. This solution was further diluted to obtain concentration 5-25 µg / ml. The diluted solutions were scanned using Shimadzu double beam UV-visible spectrophotometer from wavelength 200-400 nm range. Absorption maximum (λ max) obtained was 231 nm (Figure 6). A standard curve was plotted to study the linearity of Beer Lambert’s law (Figure 7).

Figure 6
UV spectra of cetirizine hydrochloride in simulated saliva
Aim of the present work

Table 3

**Standard curve in simulated saliva**

<table>
<thead>
<tr>
<th>Concentration (µg/ml)</th>
<th>Absorbance</th>
<th>Average Absorbance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(A)</td>
<td>(B)</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>0.252</td>
<td>0.169</td>
</tr>
<tr>
<td>8</td>
<td>0.341</td>
<td>0.246</td>
</tr>
<tr>
<td>10</td>
<td>0.383</td>
<td>0.332</td>
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<tr>
<td>12</td>
<td>0.484</td>
<td>0.379</td>
</tr>
<tr>
<td>15</td>
<td>0.631</td>
<td>0.487</td>
</tr>
<tr>
<td>20</td>
<td>0.794</td>
<td>0.624</td>
</tr>
<tr>
<td>25</td>
<td>0.98</td>
<td>0.775</td>
</tr>
</tbody>
</table>

Figure 7

Standard curve of cetirizine hydrochloride in simulated saliva

Result of regression statistics

R Square 0.999348
Intercept 0.008408
X Variable 0.031134
Aim of the present work

Equation of the line
Absorbance = Slope X Concentration + Intercept
Absorbance = 0.031134 Concentration + 0.008408
Linearity was observed between 5 to 25 µg/ml.

3.3 Evaluation of RDF-

3.3.1 Measurement of mechanical properties of the film (10, 11)
Mechanical properties of the RDF were evaluated using Lloyd universal testing machine, UK with load cell range 0-40 N. Films of dimension 10 x 2.5 cm² and free from physical imperfections were used for the study. The films were held between two clamps at distance of 5 cm. The RDF were pulled by the clamp at the rate 50 mm/min. Measurements were done in triplicate for each batch. The mechanical properties tensile strength, elastic modulus and % elongation were calculated for the RDF from the above measurements.

Tensile strength is the ratio of maximum stress applied to a point at which the film specimen breaks and can be computed from the applied force at rupture to the cross-sectional area of the fractured film as a mean of three measurements and described in the equation-

\[
\text{Tensile strength} = \frac{\text{Force at break (N)}}{\text{Initial cross sectional area of the film (mm}^2)}
\]

Elastic modulus is the ratio of applied stress and corresponding strain in the region of approximately linear proportion of elastic deformation on the load displacement profile and calculated using the following equation-

\[
\text{Elastic modulus} = \frac{\text{Force at corresponding strain (N)}}{\text{cross-sectional area of the film \times corresponding strain}}
\]

Percentage elongation was calculated by the following equation-

\[
\text{Percentage elongation} = \frac{\text{Increase in length \times 100}}{\text{Original length}}
\]

3.3.2 In-vitro disintegration studies (2, 9, 12)
Disintegration time study was slightly modified to mimic the in-vitro and in-vivo conditions. For the study, film as per the dimensions (2 x 2 cm²) required for dose delivery were placed on a stainless steel wire mesh containing 10 ml distilled water. Time required for the film to break and disintegrate was noted as in-vitro disintegration time. Since, the film is expected to disintegrate in the mouth in presence of saliva, only 10 ml of medium was used.

3.3.3 In-vivo disintegration studies (12)

The in-vivo disintegration time was measured in 6 human volunteers. The RDF was placed on the tongue of the volunteers and time required for disintegration in mouth was noted down.

3.3.4 In-vitro dissolution studies (12,13)

The in-vitro dissolution studies were conducted using three media namely distilled water (500 ml), simulated gastric fluid (900 ml) and simulated saliva (500 ml). The dissolution studies were carried out using USP dissolution apparatus XXIV (Electrolab, Mumbai, India) at 37 ± 0.5°C and at 50 rpm using specified dissolution media. Each film with dimension (2 x 2 cm²) was placed on a stainless steel wire mesh with sieve opening 700 µm. The film sample placed on the sieve was submerged into dissolution media. Samples were withdrawn at 2, 5, 10, 15, 30, 60, 120 min time intervals and filtered through 0.45 µm Whatman filter paper and were analyzed spectrophotometrically at 231 nm (UV 2450 Shimadzu, Japan). To maintain the volume, an equal volume of fresh dissolution medium maintained at same temperature was added after withdrawing samples. The absorbance values were converted to concentration using standard calibration curve previously obtained by experiment. The dissolution testing studies were performed in triplicate for all the batches.

3.3.5 Environment Scanning electron microscopy (ESEM) (14,15)

The surface morphology of the film forming excipient, drug and the film was observed using Environment scanning electron microscope (Philips, XL 30, The Netherlands). The
film sample was placed in the sample holder and the photomicrographs were taken using tungsten filament as electron source and GSE detector at 65x and 350x magnification.

3.3.6 Differential scanning calorimetry (DSC) (14,15)
DSC scans were recorded by using Differential scanning calorimeter (Perkin-Elmer, Pyris-I, MA, USA). Samples weighing 5 mg were sealed in aluminium pans and heated to 250°C at rate 10°C/min. The equipment was calibrated using indium. Samples were heated from 50 to 250°C. If required it was cooled to -10°C and then heating was continued to 250°C.

3.3.7 X Ray Diffraction (XRD) (14,15)
XRD studies of powder samples and film was performed using X Ray Diffractometer (Philips, X’pert MPD, The Netherlands) having sensitivity 0.1 mg with 40 kV voltage, 30 mA current. The sample was placed vertically at an angle of 0° in the sample chamber. An X-Ray beam (Philips Cu target x-ray tube) of 2 KW was allowed to fall over the sample. The slide was moved at an angle of theta degree, a proportional detector detected the diffracted X-Rays at angle of 2-theta degrees. XRD patterns were recorded using Philips JPCD software.

3.3.8 Taste evaluation (16)
Taste acceptability was measured by a taste panel (n=6) with 10 mg drug and subsequently film sample containing 10 mg drug held in mouth until disintegration, then spat out and the bitterness level was then recorded. The volunteers were asked to gargle with distilled water between the drug and film sample administration. The scale for the bitterness study was as follows:
+ = very bitter,
++ = moderate to bitter,
+++ = slightly bitter,
++++ = tasteless/taste masked
Aim of the present work

+++++ = excellent taste masking

3.4 References:
6. "Novartis launches first systemic OTC in film strip format".
Aim of the present work


