FORMULATION AND EVALUATION OF IRBESARTAN IMMEDIATE RELEASE TABLETS

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ABSTRACT

Irbesartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively binding to the AT1 angiotensin II receptor. ACE inhibitor is used in treatment of hypertension. Irbesartan tablet have been prepared by wet granulation method. Effect of various fillers and disintegrants were also explored. Microcrystalline cellulose, colloidal silicon dioxide, croscarmellose sodium were used in wet granulation. In order to obtain acceptable product several trials were conducted. Various pharmacopoeia evaluations of the formulations were conducted including weight variation, hardness, disintegration time, friability and in-vitro dissolution. Final selection of formulation was done based on pharmaceutical equivalence of development formulation to that of marketed one.

Keywords: Immediate release tablet, Colloidal silicon dioxide, croscarmellose sodium, hypertension.

INTRODUCTION

An ideal dosage regimen in the drug therapy of any disease is the one, which immediately attains the desired therapeutic concentration of drug in plasma (or at the site action) and maintains it constant for the entire duration treatment. This is possible through administration of conventional dosage form in particular dose and at a particular frequency. Thus drug may be administered by variety of routes in a variety of dosage forms1.

Drugs are more frequently taken by oral administration. Although a few drugs taken orally are intended to be dissolved within the mouth, the vast majority of drugs taken are swallowed. Compared with alternate routes, the oral route of drug administration is the most popular and has been successfully used for the conventional delivery of drug. It is considered most natural, uncomplicated, convenient, safe means of administering drugs, greater flexibility in dosage form design, ease of production and low cost2.

The mechanisms for release of drug from modified-release dosage forms are more complex and variable than those associated with immediate-release dosage forms. According to BCS (Biopharmaceutics classification system), there are three major factors that govern the rate and extent of drug absorption of immediate release (IR) solid oral dosage forms: dissolution rate, solubility and intestinal permeability. For IR dosage forms containing active pharmaceutical ingredients (APIs) showing high solubility, high intestinal permeability and rapid dissolution, a waiver from performing bioequivalence studies (biowaiver) can be scientifically justified3.

According to BCS classification, a drug can be classified as follows:

Class I – High solubility and high permeability.
Class II – Low solubility and high permeability.
Class III – High solubility and low permeability.
Class IV – Low solubility and low permeability.

A low solubility drug is thus one, which requires more than 250 ml water to dissolve the largest human dose and a high solubility drug is defined as one, Which at the highest human dose is soluble in 250 ml (or less) water over a pH range of 1 to 7.5 at 37°C. A jejunal permeability of at least \(2 \times 10^4\) cm²/s, measured in humans by an intubations technique, is considered high permeability4. For many substances, this permeability corresponds to a fraction absorbed of 90 % or better. The classification system provides a logical basis for estimating the risk of bioavailability problems. For example, high solubility – high permeability drugs are expected to exhibit few bioavailability problems. On the other hand, drugs having low solubility and high permeability are more likely to exhibit dissolution – rate limited absorption problems. Drugs having high solubility and low permeability are more likely to be prone to absorption rate limited absorption. Drugs having low solubility and low permeability present formidable obstacles to bioavailability5.

Irbesartan act by angiotensin II is a potent vasoconstrictor formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system (RAS) and also stimulates aldosterone synthesis and secretion by adrenal cortex, cardiac contraction, renal resorption of sodium, activity of the sympathetic nervous system and smooth muscle cell growth. Irbesartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively binding to the AT1 angiotensin II receptor. There is also an AT2 receptor in many tissues, but it is not involved in cardiovascular homeostasis6.

MATERIALS AND METHODS

Materials

The materials which were used for the formulation were of pharma grade and were obtained as a gift from different R&D centres. Irbesartan was obtained as a gift from Mission vivacare Ltd, Indore, India. Lactose monohydrate was collected from Strides Arcolab, Bangalore, India. Microcrystalline cellulose, pregelatinised starch, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate Alkem lab Mumbai.
Methods
Preformulation studies
Preformulation may be described as a phase of the research and development process where the formulation scientist characterizes the physical, chemical and mechanical properties of new drug substances, in order to develop stable, safe and effective dosage forms. Ideally the preformulation phase begins early in the discovery process such the appropriate physical, chemical data was available to aid the selection of new chemical entities that enter the development process during this evaluation possible interaction with various inert ingredients intended for use in final dosage form were also considered in the present study.

Organoleptic Properties
Colour A small quantity of Irbesartan powders were taken in butter paper and viewed in well-illuminated place.
Taste and odour Very less quantity of Irbesartan was used to get taste with the help of tongue as well as smelled to get the odour.

Determination of melting point
Melting point of the drug sample was done by open capillary method. Drug was taken in glass capillary whose one end was sealed by flame. The capillary containing drug was dipped in liquid paraffin inside the melting point apparatus. Melting point was the first indication of purity of the sample since the presence of relatively small amount of impurity can be detected by a lowering as well as widening in the melting point range.

Solubility studies
The solubility of irbesartan in phosphate buffer pH 6.8 and pH 7.4 was determined by the phase equilibrium method. An excess amount of drug was taken into 50 ml conical flasks containing 20 ml of phosphate buffers (pH 6.8 and pH 7.4). Conical flasks were closed with aluminum foil and constantly agitated at room temperature for 24 hrs using rotary shaker. After 24 hrs, the solution was filtered through filter paper. The amount of drug solubilized was then estimated by measuring the absorbance at 220 nm using a UV spectrophotometer. The standard curves for irbesartan were established in phosphate buffers (pH 6.8 and 7.4) and from the slope of the straight line the solubility of irbesartan was calculated. The studies were repeated in triplicate (n = 3), and mean was calculated.

Preparation of irbesartan immediate release tablet
First four batches prepared by direct compression method by following procedure.

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Irbesartan sifted through mesh # 16 and collected in double lined polybag. Lactose monohydrate, microcrystalline cellulose, pregelatinised starch and croscarmellose sodium sifted through mesh # 30 and added to the material. Colloidal silicon dioxide sifted through mesh # 40 and added to the material of step-2 and mixed for 10 minutes. Lubrication: Magnesium stearate through mesh # 60 and collected separately in double lined polybag.

Dry mixing
Dry mix the contents for 10 minutes.

Granulation
Granulate the dry mix of by adding purified water to that. Mix the mass to get uniform dough mass.

Drying
Dry the wet mass in tray dryer at an inlet air temperature of 60 ± 5 °C till the moisture content is NMT 2% at 105°C (measured using a halogen moisture balance). Observed LOD: 1.64%.

Sifting & Milling
Sift the dried granules using #20 sieve and collect the under size and retained granules separately. Pass the materials retained on #20 sieve.

Compression
Compress the lubricated blend of step-7 using 12.7 mm round Shaped Punches and dies, Plain on both the sides. Composition of Irbesartan immediate release tablets given in table no. 1.

Precompression parameters
Bulk density
Density is a term obtained by dividing weight of powder by volume of powder. It was given as g/cm³. Apparent bulk density was determined by pouring presieved drug excipients blend into a graduated cylinder and measuring the volume and weight. It was determined by following equation:

\[ \rho_b = \frac{m}{v_b} \]

Where, \( \rho_b \) = Bulk density, \( m \) = Mass of powder, \( v_b \) = Volume of powder

Tapped density
It was determined by placing a graduated cylinder containing a known mass of drug and excipients blend on mechanical tapping apparatus, which was operated for a fixed numbers of taps until the powder bed volume has reached a minimum using the weight of a blend in a cylinder and from this minimum volume, the tapped density was computed. It was determined by following equation:

\[ \rho_t = \frac{m}{v_t} \]

Where, \( \rho_t \) = Tapped density, \( m \) = Mass of powder, \( v_t \) = Tapped volume.

Compressibility Index
Compressibility was indirectly related to the relative flow rate, cohesiveness and particle size distribution of the powder. Powders with compressibility values lesser than about 20% have been found to exhibit good flow properties. Tapped (\( \rho_t \)) and apparent (\( \rho_a \)) bulk density measurements can be used to estimate the compressibility of a material.

Compressibility Index (%) = \( \frac{\rho_a - \rho_t}{\rho_a} \times 100 \)

Where, \( \rho_a \) = Bulk density, \( \rho_t \) = Tapped density

Hausner's ratio
It was the ratio of bulk volume to tapped volume or tapped density to bulk density. It was a measure used to describe compressibility of powder.

Hausner's ratio = \( \frac{\rho_t}{\rho_b} \)

Where, \( \rho_t \) = Tapped density, \( \rho_b \) = Bulk density
Angle of repose
The angle of repose of powder blend was determined by the funnel method. The accurately weight powder blend were taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. Angle of repose is maximum angle possible between pile of powder and horizontal plane[12].

\[
0 = \tan^{-1} \frac{h}{r}
\]

Where, \(h\) = Height of pile of powder, 
\(r\) = The radius of the base of conical pile.

Values for angle of repose less than or equal to 30° suggest a free flowing material and angles greater than or equal to 40° suggest a poorly flowing material.

Evaluation of irbesartan immediate release tablets

Thickness
Thickness of the tablets was measured using a calibrated Vernier Caliper. Three tablets of each formulation were picked randomly and thickness was measured individually.

Weight variation
Twenty tablets were selected randomly from each batch and weighed individually to check for weight variation. A little variation was allowed in the weight of a tablet according to US Pharmacopoeia[46]. The following percentage deviation in weight variation was allowed. In all formulations, the tablet weight is 120 mg, hence 7.5% maximum difference allowed[13].

Hardness
Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm². Three tablets were randomly picked and hardness of the tablets was determined.

Friability
The friability of tablets was determined by using Roche friabilator. It is expressed in percentage (%). Ten tablets were initially weighed (W_i) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W_f). The % friability was then calculated by

\[
\%F = 100 \left(1 - \frac{W_f}{W_i}\right)
\]

% Friability of tablets less than 1% was considered acceptable.

Drug content uniformity
Ten tablets were weighed and grounded in a mortar with pestle to get fine powder; powder equivalent to the mass of one tablet was dissolved in methanol by sonication for 30 min and filtered through filter paper. The drug content was analyzed spectrophotometrically at 220 nm using an UV spectrophotometer[14].

In vitro drug release of irbesartan tablets

The In vitro drug release studies of Irbesartan tablets were determined using USP II rotating paddle type. The dissolution test was performed using 1000 ml of 0.1. The N HCl release was performed at 37°C ± 0.5°C, with a rotation speed of 50 rpm[15]. The samples were filtered through filter paper and analyzed after appropriate dilution by UV spectrophotometer at 220 nm[16].

Drug excipient compatibility studies

FTIR spectroscopic studies were conducted for optimized formulation and irbesartan pure drug. Solid samples are milled with potassium bromide (KBr) to form a very fine powder. This powder is then compressed into a thin pellet under hydraulic press which can be analyzed. KBr is also transparent in the IR, the FTIR spectra were recorded between 400 and 4000 cm⁻¹[16].

Stability Studies

Stability of a drug has been defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic and toxicological specifications. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, light and enables recommended storage conditions, re test periods and shelf-lives to be established. The optimized batch of irbesartan immediate release tablet were placed in desiccators and stored at ambient conditions; such as at room temperature, oven temperature (40±2°C) with 75% RH and refrigerator (2-8°C) for a period of 60 days, then evaluated for changes in physiochemical properties, bioadhesive strength and in vitro drug release[17].

FTIR analysis

The pure drug, topiramate and a mixture of it excipients powder was mixed separately with IR grade KBr and corresponding pellets were prepared by applying 10 tons of pressure in the hydraulic press. The pellets were scanned over a wave number range of 400-4000cm⁻¹ in FTIR 8400S model instrument[18].

RESULTS AND DISCUSSION

The various formulations are prepared by using croscarmellose sodium as super disintegrant in a various concentration. In the physical evaluation of API the colour was white crystalline, odour was Characteristic odour and test was bitter. The solubility of drug was slightly soluble in ethanol (96%) and methelene chloride and practically insoluble in water.

Drug excipient compatibility studies

Drug excipients interaction was checked out by comparing the FTIR spectra of pure drug irbesartan and FTIR spectra of the physical mixture of drug and excipients. The result of FTIR spectra of pure drug irbesartan and the physical mixture of drug and excipients were shown Table02 and Figure 01 and 2 respectively.

Precompression parameter

The bulk density and tapped bulk density for all the formulation varied in range of 17.17% to 27.66% and 0.476 gm/cm³ to 0.714 gm/cm³ for all formulations lies within the range of 17.17% to 27.66% and 0.38 to 1.20 respectively. All the formulation shows acceptable compressibility and flow property showed in table no.03.

Post compression study

Tablets of all formulations (F1 to F8) were evaluated for different parameters such as thickness, hardness, weight variation, drug content and friability showed in table no.04. Physical evaluation of tablets from all batches showed flat circular shape with no cracks with white colour. The thickness of tablets ranged from 2.54 to 2.95mm. In weight variation test, the Pharmacopoeia limit for percent of deviation for tablets having weight 100mg is ±7.5%. The average percent deviation of all tablets was found to be...
within the limit and hence all formulation passes the weight variation test. The drug content was found to be uniform among all formulation and ranged from 69.50% to 99.50%. The hardness of tablets of all formulations was from 100 to 145N. The friability of tablets of all formulations ranged from 0.08% to 0.11%.

**In-vitro drug release studies**

The In-vitro dissolution data of formulation showed in table no. 05 and figure no.03, formulation F1, F2 and F3 released 73.40%, 70.37% and 69.50% drug respectively within 20 min. Formulation F4, F5 and F6 released 71.2%, 75.37% and 78.07% drug respectively within 20min. Formulation F7 and F8 released 78.67%, 99.50% and 99.061% drug respectively within 20min.

All the tablet released almost 85% of the drug within 20min, proving immediate release. Among all the formulated tablets formulation F8 containing irbesartan with croscarmellose sodium gave the highest cumulative percent released (99.57%) in 20min.

**CONCLUSION**

Development of immediate release tablet was to increase the bioavailability of drug. It may conclude that irbesartan immediate release tablet would be a promising immediate release drug for an administration. In the formulation, the combination of cost effective and biocompatible excipient had been successfully used. Total 8 formulations were formulated by wet granulation and dry granulation methods, among them formulation F8 concluded to be optimum containing croscarmellose sodium.

i. FTIR studies revealed that there are no chemical interactions between irbesartan and the excipient used in the study.

ii. Stability studies of promising formulation indicated that there was no significant changes in drug content and in vitro dissolution.

**REFERENCES**


**Table no.1: Composition of Ibesartan immediate release tablets**

<table>
<thead>
<tr>
<th>Formulation code</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>
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<tr>
<td>Ibesartan</td>
<td>300</td>
<td>300</td>
<td>300</td>
<td>300</td>
<td>300</td>
<td>300</td>
<td>300</td>
<td>300</td>
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<tr>
<td>Lactose monohydrate</td>
<td>69</td>
<td>66</td>
<td>62</td>
<td>62</td>
<td>62</td>
<td>64</td>
<td>64</td>
<td>64</td>
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<tr>
<td>Microcrystalline cellulose(RQ-102)</td>
<td>98</td>
<td>98</td>
<td>98</td>
<td>98</td>
<td>93</td>
<td>84</td>
<td>84</td>
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<tr>
<td>Croscarmellose sodium</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>12</td>
<td>28</td>
<td>31</td>
<td>24</td>
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<tr>
<td>Pregelatinised starch(Lycatab C)</td>
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<td>23</td>
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<td>23</td>
<td>23</td>
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</table>

Binder

| Water | 8 ml | 5.6 ml |

Extragranular portion

| Croscarmellose sodium | 7 | 7 | 7 |
| Collidal silicon dioxide | 10 | 10 | 10 | 10 | 5 | 5 | 5 | 5 |
| Magnesium stearate | 3 | 6 | 10 | 10 | 4 | 3 | 3 | 3 |

Total weight(mg) | 510 | 510 | 510 | 510 | 510 | 510 | 510 | 510 |
Table 02 Results of FTIR study

<table>
<thead>
<tr>
<th>Vibrations</th>
<th>Pure drug (cm(^{-1}))</th>
<th>Physical mixture (cm(^{-1}))</th>
<th>No interaction</th>
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<tr>
<td>NH Stretch</td>
<td>3400.3</td>
<td>3400.6</td>
<td></td>
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<tr>
<td>=C-H</td>
<td>3103.3</td>
<td>3103.3</td>
<td></td>
</tr>
<tr>
<td>C-N</td>
<td>1639.4</td>
<td>1641.4</td>
<td></td>
</tr>
<tr>
<td>C=C</td>
<td>1596.4</td>
<td>1590.36</td>
<td></td>
</tr>
<tr>
<td>S=O</td>
<td>1533.3</td>
<td>1533.22</td>
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<tr>
<td>C-S</td>
<td>1287.53</td>
<td>1287.53</td>
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<tr>
<td>C-N</td>
<td>1145.76</td>
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Table No.03: Evaluation of physical properties of granules

<table>
<thead>
<tr>
<th>Formulation Batches</th>
<th>Bulk density</th>
<th>Tapped density</th>
<th>Carr’s index</th>
<th>Hausner ratio</th>
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<tbody>
<tr>
<td>F1</td>
<td>0.53 gm/cc</td>
<td>0.73 gm/cc</td>
<td>27.66%</td>
<td>1.38</td>
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<tr>
<td>F2</td>
<td>0.526 gm/cc</td>
<td>0.714 gm/cc</td>
<td>26.94%</td>
<td>1.34</td>
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<tr>
<td>F3</td>
<td>0.518 gm/cc</td>
<td>0.689 gm/cc</td>
<td>24.91%</td>
<td>1.33</td>
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<td>F4</td>
<td>0.518 gm/cc</td>
<td>0.671 gm/cc</td>
<td>23.62%</td>
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<tr>
<td>F5</td>
<td>0.487 gm/cc</td>
<td>0.625 gm/cc</td>
<td>22.08%</td>
<td>1.28</td>
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<tr>
<td>F6</td>
<td>0.483 gm/cc</td>
<td>0.630 gm/cc</td>
<td>23.38%</td>
<td>1.30</td>
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<tr>
<td>F7</td>
<td>0.476 gm/cc</td>
<td>0.588 gm/cc</td>
<td>19.04%</td>
<td>1.23</td>
</tr>
<tr>
<td>F8</td>
<td>0.487 gm/cc</td>
<td>0.588 gm/cc</td>
<td>17.17%</td>
<td>1.20</td>
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Table no.04: Standard physical tests for irbesartan immediate release tablet

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<tr>
<th>Formulation batches</th>
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<tr>
<td></td>
<td>Wt. variation</td>
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<tr>
<td>F1</td>
<td>494-546</td>
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<tr>
<td>F2</td>
<td>496-541</td>
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<td>F3</td>
<td>497-543</td>
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<td>501-547</td>
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<td>F8</td>
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Table No: 05 Percentage drug release

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<tr>
<th>Time(min)</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
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<tr>
<td>5</td>
<td>17.83</td>
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<tr>
<td>10</td>
<td>34.83</td>
<td>32.87</td>
<td>33.50</td>
<td>35.53</td>
<td>40.24</td>
<td>40.67</td>
<td>69.67</td>
<td>86.97</td>
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<tr>
<td>15</td>
<td>55.03</td>
<td>53.23</td>
<td>52.23</td>
<td>53.10</td>
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<td>60.30</td>
<td>60.97</td>
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<tr>
<td>20</td>
<td>73.40</td>
<td>70.37</td>
<td>69.50</td>
<td>71.20</td>
<td>75.37</td>
<td>78.07</td>
<td>78.67</td>
<td>99.50</td>
</tr>
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</table>

Figure 01: FTIR Spectrum of irbesartan
Figure 02: FTIR Spectrum for physical mixture of drug and excipients

Fig no. 03: % Drug Release of formulations

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