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# Formulation and Evaluation of Immediate Release Tablets of Irbesartan

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**A B S T R A C T**

The aim of the present study is to formulate and evaluate immediate release tablets of irbesartan by using wet granulation method. The tablets were prepared by varying concentrations of crosscarmellose sodium, sodium starch glycolate, crospovidone, mannitol, meglumine. The drug polymer compatability were studied by FTIR studies. No significant drug polymer interactions were observed in FTIR studies. The tablets were evaluated for disintegration time, content uniformity, friability, water absorption ratio. *In-vitro* drug release profile of irbesartan was examined in pH 0.1N Hydrochloric acid for 30 mins. The formulation f4 showed immediate release and all evaluation tests carried were within limits.

**Keywords:** Irbesartan, croscarmellose sodium, sodium starch glycolate, crospovidone, meglumine.

**A R T I C L E I N F O**

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## 1. Introduction

Oral administration is the most popular route for systemic effects due to its ease of ingestion, pain avoidance, versatility and most importantly, patient compliance. Also solid oral delivery systems do not require sterile conditions and are therefore, less expensive to manufacture. Patient compliance, high-precision dosing and manufacturing efficiency make tablets the solid dosage form of choice. The developments of enhanced oral protein delivery technology by immediate release tablets which may release the drugs at an enhanced rate are very promising for the

delivery of poorly soluble drugs high molecular weight protein and peptide. The oral route remains the perfect route for the administration of therapeutic agents because the low cost of therapy, manufacturing and ease of administration lead to high levels of patient compliance [1, 2]. Many patients require quick onset of action in particular therapeutic condition and consequently immediate release of medicament is required. It is estimated that 50% of the population is affected by this problem, which results in a high incidence of ineffective therapy [3].

The concept of immediate release drug delivery system emerged from the desire to provide patient with more conventional means of taking their medication. It is difficulty for many patients to swallow tablets and hard gelatin capsules [4]. Hence, they do not comply with prescription, which results in high incidence of non-compliance and ineffective therapy. In some cases such as motion sickness, sudden episodes of allergic attacks or coughing and unavailability of water, swallowing conventional tablets may be difficult [5]. Such problems can be resolved by means of immediate release tablets when put on tongue these tablets disintegrate and dissolve rapidly in saliva without need of drinking water. The faster the drug disintegrates in to solution, the quicker the absorption and onset of clinical effect. Some drugs are absorbed from the mouth, pharynx and oesophagus as saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablets dosage form [6, 7]. Irbesartan is an angiotensin II receptor antagonist used mainly for the treatment of hypertension. Irbesartan may also delay progression of diabetic nephropathy and is also indicated for the reduction of renal disease progression in patients with type 2 diabetes and microalbuminuria (>30 mg/24 hours) or proteinuria (>900 mg/24 hours). It belongs to BCS class II drug, which has low solubility and high permeability. It has the oral bioavailability of 60-80% and the half life of the drug is 11-15hours [8, 9]. The present work is aimed at developing the immediate release tablets of Irbesartan increase the solubility and dissolution of the drug.

## 2. Material and methods

**Materials:** Irbesartan was obtained as a gift sample from Torrent Pharma. Microcrystaline sodium, mannitol, croscaramellose sodium, sodium starch glycolate, crospovidone, aspartate, magnesium stearate were purchased from SD Fine Chem Pvt Ltd, Mumbai. Meglumine was purchased from Sigma Aladrich.

**Methods:**

**Fourier Transformation Infra-red (FTIR) analysis:** Determine of incompatibility between drug and various excipients was performed by Fourier Transformation Infrared Spectrophotometer Alpha Brooker FTIR (Tokyo, Japan).The instrument was calibrated by using polystyrene film.

**Formulation development**

Irbesartan immediate release tablets were prepared by direct compression method. All the ingredients were weighed as mentioned in table-1 (except Mg.Stearate) and sifted through # 44 mesh separately. The ingredients after sifting through sieve no. 44 were thoroughly mixed by geometrical order and mixed for 10 min. And finally glidant (Magnesium Stearate) is added to the above blend and mix it for 2min. The above lubricated blend is compressed by using 8mm round punches.

**Table 1:** Composition of Irbesartan Tablets

| Ingredients (mg) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | F10 | F11 | F12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Irbesartan | 150 | 150 | 150 | 150 | 150 | 150 | 150 | 150 | 150 | 150 | 150 | 150 |
| Croscarmellose sodium | 10 | 20 | --- | --- | --- | --- | 10 | 10 | --- | 5 | 5 | 5 |
| Sodium Starch Glycolate | --- | --- | 10 | 20 | --- | --- | --- | 10 | 10 | 5 | 10 | 5 |
| Crospovidone | --- | --- | --- | --- | 10 | 20 | 10 | --- | 10 | 10 | 5 | 10 |
| Meglumin | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| Microcrystalline Cellulose 102 | Q.S | Q.S | Q.S | Q.S | Q.S | Q.S | Q.S | Q.S | Q.S | Q.S | Q.S | Q.S |
| Mannitol | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| Aspertame | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Magnesium stearate | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Total weight(mg) | 300 | 300 | 300 | 300 | 300 | 300 | 300 | 300 | 300 | 300 | 300 | 300 |

**Precompression parameters:** The powder blend of the formulations are subjected to precompression parameters such as bulk density, tapped density, carrs index, hausner's ratio and angle of repose to determine the nature of its flow and its compressibility nature [10].

**Post Compression Parameters:**

The quantitative evaluation and assessment of tablets chemical and physical properties are important in the design of tablets and to monitor product quality. There are various standards that have been set in the various pharmacopoeias regarding the quality of pharmaceutical tablets. These include the diameter, size, shape, thickness, weight, hardness, disintegration and dissolution characters [11].

**Thickness:**

It can be dimensionally described & controlled. The thickness of a tablet is only variables. Tablet thickness is

measured by vernier callipers. Tablet thickness should be controlled within ± 5% variation of standard value.

**Weight variation test:**

This is an in process quality control test to ensure that the manufacturers control the variation in the weight of the compressed tablets, different pharmacopoeia specify these weight variation tests. Twenty tablets were weighed individually and the average weight was calculated. The individual tablet weights are then compared to the average weight. Not more than two tablets should differ in their average weight by more than percentages stated in USP. No tablet must differ by more than double the relevant percentage.

**Table 2:** Limits for Tablet Weight variation test

| Average weight of tablet (mg) | % Difference allowed |
|---|---|
| 130 or less | 10 % |
| From 130 to 324 | 7.5 % |
| > 324 | 5 % |

**Friability**:

Twenty tablets were weighed and placed in the apparatus where they are exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. After four minutes of this treatment or 100 revolutions, the tablets are weighed and the weight compared with the initial weight. The loss due to abrasion is a measure of the tablet friability. The value is expressed as a percentage. A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test is considered generally acceptable and any broken or smashed tablets are not picked. The percentage friability was determined by the formula

$$\%\ Friability = \frac{W_1 - W_2}{W_1} \times 100$$

Where

$W_1$ = Weight of tablets before test

$W_2$ = Weight of tablets after test

**Content Uniformity:**

The content uniformity test is used to ensure that every tablet contains the amount of drug substance intended with little variation among tablets within a batch. 10 tablets were taken in mortar and powdered, then quantity of powder equivalent to one tablet was transferred into 100 ml volumetric flask and 10 ml of ethanol was added and shaken for 30 min, the volume was made up to the mark with pH 1.2 HCl buffer. The above solution was suitably diluted and assayed for Irbesartan content by measuring absorbance at 220 nm using UV- Spectrophotometer (UV – 3092) [12].

**Wetting time:**

Five circular tissue papers of 10cm diameter were placed in a petridish with a 10cm diameter. 10 ml of water at 37°C ± 0.5°C containing eosin, a water-soluble dye, was added to the petridish. A tablet was carefully placed on the surface of tissue paper. The time required for water to reach the upper surface of the tablets was noted as the wetting time. Six tablets from each formulation batch were tested randomly and the average reading noted [13].

**Water absorption ratio:**

A piece of tissue paper folded twice was placed in a small Petri dish containing 6ml of water. A tablet was put on the paper and the time required for complete wetting was measured [13]. The wetted tablet was then weighed. Water absorption ratio R, was determined using following equation

$$R = \frac{W_a - W_b}{W_b} \times 100$$

Where

$W_a$ = weight of tablet after absorption,

$W_b$ = weight of tablet before absorption.

**Disintegration time:**

To test for disintegration time, one tablet is placed in each tube and the basket rack is positioned in a 1-L beaker of water, simulated gastric fluid or simulated intestinal fluid at 37 ± 2° C such that the tablet remain 2.5 cm below the surface of liquid on their upward movement and not closer than 2.5 cm from the bottom of the beaker in their downward movement. Move the basket containing the tablets up and down through a distance of 5-6 cm at a frequency of 28 to 32 cycles per minute. Floating of the tablets can be prevented by placing perforated plastic discs on each tablet. According to the test the tablet must disintegrate and all particles must pass through the 10 mesh screen in the time specified. If any residue remains, it must have a soft mass. If one or two tablets fail to disintegrate, the test is repeated using 12 tablets [14,15].

**Drug release**

The drug release from the Irbesartan tablets was investigated in a USP-II(paddle) apparatus, 900 ml of 0.1N HCl (50 rpm, 37°C). At predetermined time intervals, 5-ml samples were withdrawn and from that 1ml sample was taken and diluted to 10 ml and then analyzed with UV spectrophotometry at 220 nm to determine the amount of drug released [16].

## 3. Results and Discussion

**Fourier Transformation Infra-red (FTIR) analysis:**

The comparative FTIR studies of Drug and excipients combination had shown negligible variation in the values as compared with that of only pure form of Drug. Therefore it implies good compatibility of drug and excipients. The spectras obtained are given in figures 1 and 2.

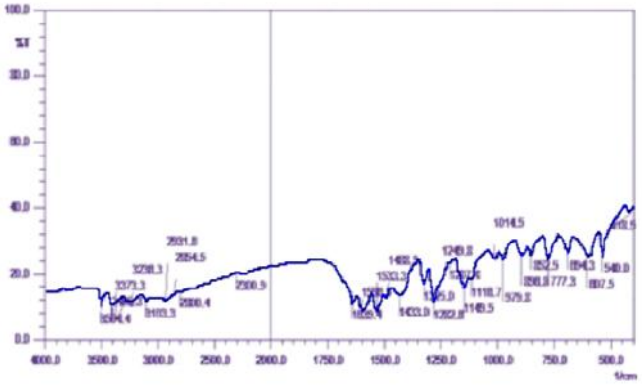

**Figure1:** FT-IR spectrum for irbesartan (pure drug)

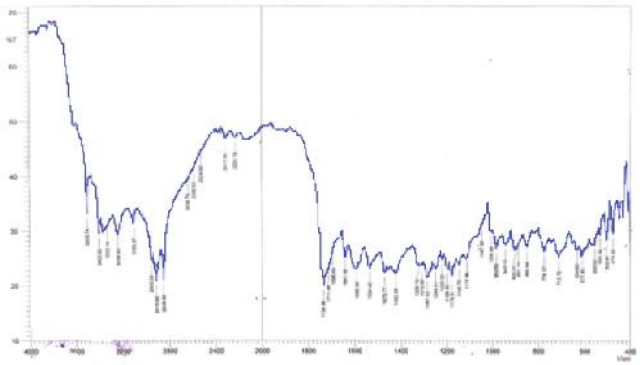

**Figure 2:** FT-IR spectrum of drug along with excipients

**Precompression studies:**

The bulk density of all formulations was found in the range of (0.37 to 0.42**)** and tapped density was in range of (0.43 to 0.47**)**. The carr's index and hausner's ratio was calculated from tapped density and bulk density. The powder blend of all formulations with hausner's ratio < 1.2 and carr's index < 17 indicates good flow ability of all powder blends. The flow properties for all the powder blends were good as evidentially proved by the angle of repose values obtained, which are less than 30°. The results are given in the table.3

**Post compression studies:**

The hardness of the all formulations was found to be 3.3 to 4.1 kg/cm$^2$ and friability was found to be below 1% indicating good mechanical resistance. The thickness of the tablets was found to be 1.85 to 1.98mm. All the tablets passed weight variation test, as percentage weight variation was within the pharmacopoeial limits i.e. ±7.5%. The drug content was found to be 97.54 to 104.21% indicating uniform distribution of drug in the tablets.

**Table 3:** Precompression studies of blend of all formulation

| Formulation | Bulk density (gm/cm$^3$) | Tapped density (gm/cm$^3$) | Angle of repose(θ) | Carr's Index (%) | *Hausner's* ratio |
|---|---|---|---|---|---|
| F1 | 0.40 | 0.47 | 21.5 | 14.89 | 1.17 |
| F2 | 0.41 | 0.46 | 20.1 | 12.1 | 1.12 |
| F3 | 0.41 | 0.47 | 19.6 | 12.7 | 1.14 |
| F4 | 0.41 | 0.45 | 20.1 | 8.8 | 1.09 |
| F5 | 0.39 | 0.45 | 21.3 | 13.3 | 1.15 |
| F6 | 0.38 | 0.46 | 19.5 | 17.3 | 1.21 |
| F7 | 0.37 | 0.43 | 19.2 | 13.9 | 1.16 |
| F8 | 0.41 | 0.46 | 17.5 | 10.8 | 1.12 |
| F9 | 0.40 | 0.45 | 21.9 | 11.1 | 1.12 |
| F10 | 0.42 | 0.47 | 19.4 | 10.6 | 1.11 |
| F11 | 0.39 | 0.44 | 19.6 | 11.3 | 1.12 |
| F12 | 0.38 | 0.43 | 18.8 | 11.6 | 1.13 |

**Table 4:** Post compression evaluation of tablets

| Formulation Code | Weight Variation | Hardness Kg/Cm$^2$ | Thickness (Mm) | Friability (%) | Content Uniformity (%) |
|---|---|---|---|---|---|
| F1 | 298±0.13 | 3.6 | 1.85 | 0.15% | 104.21 |
| F2 | 294±0.53 | 3.5 | 1.9 | 0.12% | 99.72 |
| F3 | 299±0.69 | 4.1 | 1.91 | 0.14% | 97.54 |
| F4 | 300±0.11 | 3.9 | 1.95 | 0.12% | 102.98 |
| F5 | 295±0.16 | 3.5 | 1.86 | 0.13% | 99.56 |
| F6 | 302±0.17 | 3.3 | 1.92 | 0.12% | 99.62 |
| F7 | 298±0.18 | 3.4 | 1.91 | 0.14% | 101.18 |
| F8 | 298±0.10 | 3.8 | 1.93 | 0.16% | 99.81 |
| F9 | 294±0.03 | 3.5 | 1.87 | 0.15% | 98.64 |
| F10 | 295±0.04 | 3.7 | 1.98 | 0.13% | 98.73 |
| F11 | 294±0.89 | 3.4 | 1.91 | 0.14% | 99.46 |
| F12 | 301±0.03 | 3.8 | 1.92 | 0.19% | 99.37 |

**Table 5:** Specific evaluation results for immediate release tablets of irbesartan

| Formulation code | Disintegration time (sec) | Wetting time (sec) | Water Absorption Ratio |
|---|---|---|---|
| F1 | 20 | 15 | 24.95 |
| F2 | 18 | 14 | 24.39 |
| F3 | 16 | 12 | 19.5 |
| F4 | 12 | 8 | 16.82 |

| | | | |
|---|---|---|---|
| F5 | 19 | 10 | 27.94 |
| F6 | 17 | 12 | 16.36 |
| F7 | 15 | 15 | 14.54 |
| F8 | 13 | 11 | 19.81 |
| F9 | 20 | 12 | 27.92 |
| F10 | 18 | 14 | 22.39 |
| F11 | 16 | 12 | 19.57 |
| F12 | 13 | 9 | 24.84 |

**Table 6:** Dissolution profile of prepared formulations

| **Time (mins)** | **Cumulative % drug release** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **F1** | **F2** | **F3** | **F4** | **F5** | **F6** | **F7** | **F8** | **F9** | **F10** | **F11** | **F12** |
| 0 | 0 | 0 | 0 | **0** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 5 | 12.69 | 16.58 | 20.46 | **30.56** | 15.69 | 19.58 | 24.46 | 28.56 | 11.69 | 15.58 | 21.46 | 26.69 |
| 10 | 34.65 | 41.64 | 43.46 | **52.35** | 35.65 | 41.64 | 45.46 | 49.35 | 31.72 | 38.64 | 43.43 | 45.65 |
| 15 | 53.64 | 64.64 | 67.46 | **76.65** | 57.64 | 64.64 | 65.46 | 67.65 | 57.38 | 60.64 | 63.46 | 67.64 |
| 20 | 68.49 | 78.63 | 80.64 | **87.64** | 68.49 | 78.63 | 82.64 | 84.64 | 72.49 | 78.63 | 81.64 | 83.49 |
| 30 | 79.65 | 84.54 | 88.65 | **99.82** | 81.65 | 86.54 | 95.65 | 98.12 | 82.65 | 86.54 | 92.65 | 94.65 |

Disintegration times of all batches were found in the range of 12 to 20 sec fulfilling the official requirements (less than1 min) for immediate release tablets. The wetting time of the formulated tablets were found in the range of 8 to 15 sec. Water absorption ratio was increased and disintegration time was decreased with an increase in concentration of superdisintegrants.

***In-vitro* dissolution studies:**

The results of *in-vitro* dissolution studies were given in table-6. F1 and F2 formulations containing Croscarmellose sodium alone have a drug release of 76.65% and 84.54%. F3 and F4 formulations containing Sodium Starch Glycolate have shown a drug release of 88.65 and 99.82%. F5 and F6 formulations containing Crospovidone have shown a drug release of 81.65 and 86.54%. It was found that as disintegrant concentration is increased, the time required for the complete drug release has been reduced or more amount drug release is been observed as concentration increased. F7 formulation containing Crospovidone and Croscarmellose sodium in 1:1ratio have shown a drug release of 95.65%. F8 formulation containing Sodium Starch Glycolate and Croscarmellose sodium in 1:1ratio have shown a drug release of 98.12%. F9 formulation containing Sodium Starch Glycolate and Crospovidone in 1:1ratio have shown a drug release of 82.65%. F10 formulation containing Croscarmellose sodium, Sodium Starch Glycolate and Crospovidone in 0.5:0.5:1ratio have shown a drug release of 86.54%. F11 formulation containing Croscarmellose sodium, Sodium Starch Glycolate and Crospovidone in 0.5:1:0.5 ratios have shown a drug release of 92.65%. F12 formulation containing Croscarmellose sodium, Sodium Starch Glycolate and Crospovidone in 1:0.5:0.5 ratios have shown a drug release of 94.65%. On comparing the results obtained with different combinations and concentrations it was found that formulation F4 containing Sodium Starch Glycolate alone have shown a maximum drug release at 30mins and the disintegration time of this formulation was found to be 12sec. Thus formulation F4 is optimized.

## 4. Conclusion

The formulations were successfully developed using various disintegrants like croscarmellose sodium, sodium starch glycolate and Crospovidone. From the excuted experimental results it could be confirmed that croscarmellose sodium, sodium starch glycolate and crospovidone are suitable carriers for Irbesartan. FTIR studies revealed that there are incompatibilities between the drug and excipients used in the formulations. The precompression evaluation studies have shown that the powder blend has good flow properties and are suitable for direct compression. Post compression evaluation studies have shown that all the parameters were within the specifications for immediate release formulations. Of all the formulations developed formulation F4 was optimized based on the results of disintegration time, wetting time, water absorption ratio and *in-vitro* dissolution profiles. It releases maximum of drug within 30mins there by the objective of increasing dissolution has been met by this formulation.

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