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Formulation and Evaluation of Controlled Release Tablet of Irbesartan

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Abstract: The main aim of present work was to formulate and evaluate controlled release matrix tablets of Irbesartan. It releases drugs at fixed and expected rate in a controlled manner either by dissolution and diffusion control mechanism. The matrix tablet was prepared by wet granulation method using by various concentration of HPMC and ethyl cellulose with combination of various release retardant polymer. The powder mixtures were subjected to various pre- compression parameters such as angle of repose, bulk density, tapped density and Carr's index shows satisfactory result and the compressed tablets are evaluated for post- compression parameters such as weight variation, thickness, hardness, friability, drug content and in- vitro dissolution studies. In- vitro dissolution studies were carried out for 24 hours using 0.1N HCL for first 2 hours and ph 6.8 phosphate buffers for 24 hours and the result showed that formulations F3 and F4 show good dissolution profile to control the drug release respectively. The drug content of the formulation was determined by using 0.1 N HCL at 262nm. The drug content was maximum with formulation F5 and minimum with formulation F3.
Keywords: Controlled release, Matrix tablets, Irbesartan, HPMC

Introduction-

Tablets are one of the well-known and conventional oral solid dosage forms. First tablet was formulated by hand operated device in 1843. Tablets can be divided into various categories like core (uncoated), coated (sugar and film coating), dispersible, effervescent, chewable, sublingual, buccal, and modifies release tablets (delayed, prolonged sustained and controlled release tablets). [1]

The first oral controlled drug release delivery system was developed by Israel lipowski in 1938, who worked on coated pellets. The oral sustained release delivery system developed in 1940, and the development of controlled release system in 1950. Drug delivery is generally influenced by disintegration and dissolution of matrix in which the active pharmaceutical ingredient is blended. [2]

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Controlled release dosage form covers a wide range of prolonged action formulations which provides continuous release of their active ingredients at a predetermined rate and for a predetermined time. The majority of these formulations are designed for oral administration.[2]

Materials and Method-

Materials- Irbesartan was obtained from Sun pharma dewas (MP). HPMC, PVP and Magnesium stearate obtained from SDFCL. Ethyl cellulose and lactose was obtained from Himedia.

Methods-

Preformulation Study- [4, 5]

1. **Organoleptic Properties-** The pure drug sample was studied for their organoleptic properties like colour, odour, taste, crystallinity and pH.

2. **Determination of Melting point-** Melting point of drug sample was determined by using melting point apparatus. Drug sample was filled in one end open capillary tube. The capillary was placed in melting point apparatus and gradually temperature rises when drug sample were melted the melting point of sample powder was recorded.

3. **Determination of λmax by UV spectroscopy-** 10 mg of drug was accurately weight and dissolve in 10 ml of 0.1N HCL in a 100 ml volumetric flask and then volume make up to 100 ml with 0.1N HCL to give 1000µg/ml solution. 10 ml of the above solution was pippeted out in a volumetric flask and diluted up to the mark to give 100µg/ml solution. From this 1 ml of solution was pippeted out and transferred into a 10 ml of volumetric flask and diluted up to the mark with 0.1N HCL to form 10µg/ml that was scanned in the range of 200-400 nm using UV- visible double beam spectrophotometer (shimadzu 1800).

4. **Preparation of Calibration Curve-**

   Preparation of standard stock solution- Standard stock solution was prepared by transferring 100mg of accurately weighed irbesartan to a 100 ml volumetric flask and adding 0.1 N HCL as a solvent up to the mark to give 1000µg/ml.

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10 ml of 1000 µg/ml stock solution was transferred to a 100 ml of volumetric flask and volume was made up to the mark to give 100µg/ml solution as standard working solution.

Preparation of working solution- A series of concentrations ranging from 2-10µg/ml was prepared by pipetting out 0.2, 0.4, 0.6, 0.8 and 1 of standard working solution to different 5 volumetric flasks volume made up to 2-10µg/ml.

Preparation of standard plot- Observed absorption maxima, λmax 262nm was used for further analysis of absorption for concentration ranging from 2 to 10µg/ml. The linear plot was constructed and correlation coefficient (r^2) value was determined. The result was plotted.

5. **Partition coefficient-** The partition coefficient determination of Irbesartan was performed using n-octanol as the oil phase and water (1:1) as the aqueous phase. The two phases were mixed in equal quantities (50 ml) by adding 50mg of drug in a separating funnel and was saturated with each other at room temperature for 24 hour to separate the two phases. The test compound in each phase was sample and quantitated using UV spectroscopy. The ratio of obtained concentration in octanol phase to the concentration in buffer phase was determined and the log10 of the ratio was calculated.

6. **Solubility Analysis-**

Quantitative solubility- The solubility of irbesartan in various medium was determined by equilibrium solubility method. In this method 5 ml of each solvent was taken into a separate vial and excess amount of irbesartan was added to each solvent and stirred magnetically. After stirring for 24 hours at 37˚C, the equilibrate sample were centrifuged for 10 min. at 5000rpm. Supernatant was filtered and properly diluted with water. Concentration of irbesartan was determined by UV spectroscopy.

Qualitative solubility- In this method dissolving 10 mg of drug in 10 ml of solvent and was stirred magnetically. Different solvents were used for the solubility determination like (Distilled water, Ethanol, Methanol, Dichloromethane, 0.1N HCL, Chloroform, 0.1N NaOH, pH 3.0 citrate buffers, and pH 6.8 phosphate buffer). After stirring for 24 hours at 37˚C, the equilibrated sample was visually inspected.

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Formulation of tablet preparation of controlled release matrix tablet- [8]

Controlled release tablet were prepared by wet granulation method. The tablets were prepared by wet granulation method. The different steps involved in the process are: All the raw materials were passed through sieve no. 60 and weighed accurately as per the formulae reported in table irbesartan, Polymers (HPMC and Ethyl cellulose), PVP, Aerosol and Lactose were mixed thoroughly by triturating in mortar and pestle to get uniform mix. The thoroughly mixed powder was needed for 10 minutes with Isopropyl alcohol solution till it forms dough mass. This mass was passed through sieve no. 20 to form granules. The granules were spread on the tray and kept for drying at 50°C for 30min using hot air oven. The dried granules were passed through the sieve no. 40 to get fines and uniform sized granules and homogenized with magnesium Stearate.

Table No.1: Composition of different formulation batches (%w/w)

S. NO.	Ingredients	F1	F2	F3	F4	F5
1.	DRUG	50	50	50	50	50
2.	HPMC	50	100	0	40	60
3.	Ethyl cellulose	50	0	100	60	40
4.	PVP	5	5	5	5	5
5.	Mg. Stearate	4	4	4	4	4
6.	Aerosol	1	1	1	1	1
7.	Lactose	40	40	40	40	40
8.	Total weight	200	200	200	200	200

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Evaluation of Pre Compression Parameters- [6]

- **Bulk density and Tapped study-** 20 g of the mixed blend (W) was introduced into a 100 ml measuring cylinder, and the initial volume was observed. The cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 sec intervals. The tapping was continued until no further change in volume was noted.

The bulk density, and tapped density were calculated using the following formulae.

Bulk density= W/ VO

Tapped density= W/VF

Where, W = weight of the powder mixture, VO = initial volume of the powder mixture and VF = final volume of the powder mixture.

- **Carr's index-**

These percentage and ratio are determined by using following formula:

Carr's index (%) = [(Tapped density – Bulk density) x 100] / Tapped density

- **Angle of repose-**

The slope of heap is checked by fixed funnel method. The height and diameters of conical pile is measured and angle of repose (Θ) is obtained by:

Θ = tan-1 (h / r)

h = height of cone

r = radius of conical base

Evaluation of Post Compression Parameters- [7, 8]

The tablets of different formulations were subjected to various evaluation tests, such as Thickness, uniformity of weight, hardness, friability, drug content and In vitro drug release.

- **Hardness-** The resistance of tablets to shipping or breakage under conditions of storage, transportation and

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handling before usage depends on its hardness. The hardness of each batch of tablet was checked by using Monsanto hardness tester. The hardness was measured in terms of kg/cm^2. 5 tablets were chosen randomly and tested for hardness. The average hardness of 5 determinations was recorded.

- **Thickness-** Thickness of the tablet is important for uniformity of tablet size. Thickness was measured using Vernier Callipers. It was determined by checking the thickness of ten tablets of each formulation batch.

- **Weight variations-** The weight of the tablet being made was routinely determined to ensure that a tablet contains the proper amount of drug. The USP weight variation test is done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average. The tablets met the USP specification that not more than 2 tablets are outside the percentage limits and no tablet differs by more than 2 times the percentage limit.
- **Drug Content-** Drug content was determined by dissolving the prepared tablet of irbesartan drug in 100 ml of phosphate buffer pH 6.8 .The aliquot of 1ml was taken and diluted to 10ml with distilled water. Then solution was filtered through whatman filter paper and solution was analyzed on UV spectrophotometer at desired wavelength to calculate the amount of drug present in the tablet.
- **Friability-** 20 tablets were weighed and the initial weight of these tablets was recorded and placed in Roche friabilator and rotated at the speed of 25 rpm for 100 revolutions. Then tablets were removed from the friabilator dusted off the fines and again weighed and the weight was recorded. Percentage friability was calculated by using the formula:

% Friability = [(W1 – W2) x 100] / W1

Where, W1= Initial weight of the tablets

W2= Final weight of the tablets

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- **In- Vitro drug release-**

The in-vitro dissolution profile of the designed formulations of controlled release tablets was carried out using USP type II apparatus under conditions specified (temp 37± 0.50C, 75rpm). Tablets were subjected to dissolution 0.1 N HCl for six hrs till the end of dissolution studies. From the dissolution medium 1ml solution was withdrawn and replaced 1 ml for every 5 min. The solution withdrawn volume was made up to 10 ml with distilled water and absorbance was measured at 262 nm using distilled water as blank. Dissolution profiles of the formulations were analyzed by plotting drug release versus time plot.

Result and Discussion-

Preformulation Studies-

1) Organoleptic Properties-

The drug was studied for their organoleptic properties like colour, odour, taste, crystallinity and pH observation was recorded in Table 2

Table 2: Organoleptic Properties of Irbesartan

Parameters	Result
Colour	White
Odour	Odour
Taste	Extremely bitter in taste
Crystallinity	Crystalline in nature
pH	4.6

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2) Melting point-

The melting point of the drug is found in 180^0 C-184^0 C range and crystalline in nature of drug. Which approx. same as reported in I.P. 2018 so it shows the purity of the drug.

3) Determination of λmax by UV spectroscopy-

Identification of drug was also carried out using UV Visible Spectrophotometer. HCL was used as the medium and observed absorption maxima were compared with the reported with the reported value. The wavelength of maximum absorbance acts as a characteristic value for a compound. Observed value for the obtained sample of pure Irbesartan was 262nm fount to be identical to the reported value that confirmed the obtained sample as Irbesartan.

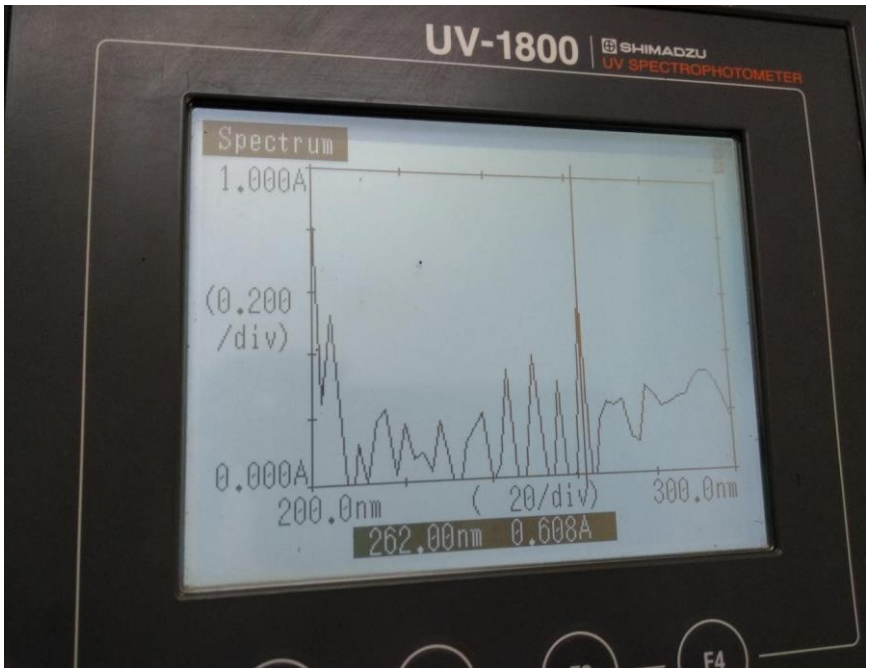

Fig 1: Determination of λmax is 262nm

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4) Preparation of Calibration Curve-

The wavelength of maximum absorbance, λmax for irbesartan in HCL was determined with the help of UV-Visible Spectrophotometer. Prepared solution of concentration 15mg/ml was scanned in the range of 200-400nm. The λmax observed was 262nm. Observed absorption maxima, λmax 262nm was used for further analysis of absorption for concentration ranging 2-10µg/ml. The linear plot was obtained and concentration range 2-10µg/ml and correlation coefficient (r2) value was found to be 0.998. The results were plotted as in fig. 2.

Table 3: Absorbance data of Irbesartan for preparation of Calibration curve-

S. No.	Concentration (µg/ml)	Absorbance
1.	0.2	0.203
2.	0.4	0.412
3.	0.6	0.612
4.	0.8	0.813
5.	1	0.974

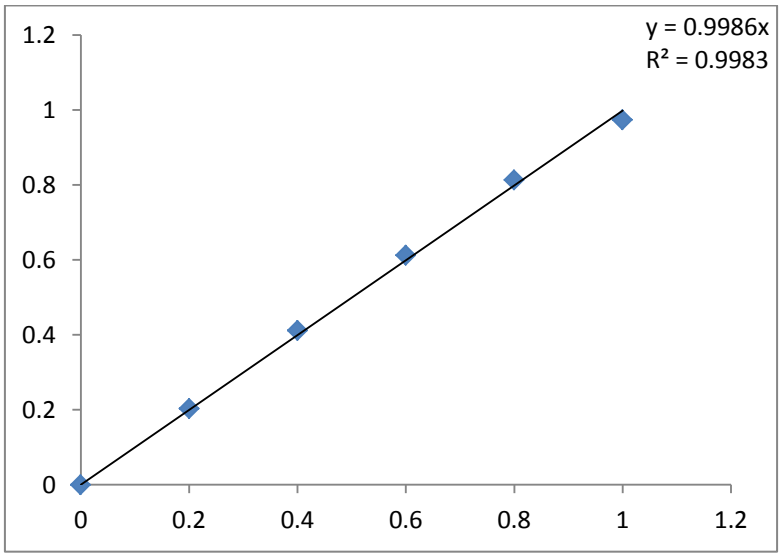

Fig 2: Calibration curve of Irbesartan

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5) Partition Coefficient-

Log_{10} P is the logarithmic value of partition coefficient (p), the ratio of an amount of solute in the organic phase to aqueous phase that helps to determine the partition coefficient of drug. In this research partition coefficient of drug was determine by interpreting the value of log p calculated from calibration curve equation. The value for log_{10} P was obtained as 5.64 close to the reported value of 5.98. The result reflected the lipophilic nature of drug and thus Irbesartan found to have high permeability.

6) Solubility Analysis-

Quantitative Solubility- The solubility of Irbesartan in various medium was studied and the result of study were shown in table 4

Table 4: Quantitative solubility of Irbesartan

Solvents (10ml)	**Solubility (mg/ml) Mean±SD**
Methanol	0.780
Ethanol	0.540
0.1 N HCL	1.230
Chloroform	1.190
Dichloromethane	0.230
0.1 N NaoH	1.170
pH 3.0 citrate buffer	0.164
pH 6.8 phosphate buffer	0.848
Water	<0.1

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Qualitative Solubility-

The solubility of irbesartan in various medium was studied and the result of study were shown in table 5

Table 5: Qualitative solubility of Irbesartan-

Solvents	**Solubility**
Methanol	Springly Soluble
Ethanol	Soluble
0.1 N HCL	Soluble
0.1 N NaoH	Soluble
Chloroform	Soluble
Dichloromethane	Soluble
Water	Practically insoluble

Evaluation of Pre Compression Parameter-

Evaluated of pre compression parameters, they includes - Bulk density, Tapped density, Carr's Index, Angle of Repose shown in table no. 6

Table No.6: Evaluation parameters of Optimized matrix tablets

S.NO.	**Formula**	**Bulk density**	**Tapped density**	**Carr's index**	**Angle of repose**
1.	F1	0.46±0.00	0.53±0.00	14.16±0.03	26.79±1.15
2.	F2	0.41±0.00	0.49±0.00	18.54±0.03	27.86±0.22
3.	F3	0.47±0.00	0.52±0.00	10.54±0.01	22.86±0.22
4.	F4	0.47±0.00	0.56±0.00	10.54±0.01	22.88±1.08
5.	F5	0.38±0.00	0.56±0.00	14.85±0.04	26.80±1.09

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Evaluation of post-compression parameters-

The tablets of different formulations were subjected to various evaluation tests, such as thickness, uniformity of weight, hardness, friability, and drug content and the result are shown in Table No.7.

Table No.7: Post-compression parameters of matrix tablets

S.NO.	Formula	Weight variation	Drug content	Hardness (kg/cm2)	Thickness (mm)	% friability
1.	F1	195±1.02	49.32	2.55±0.40	4.19±0.02	0.10±0.00
2.	F2	193±1.32	47.52	2.98±0.32	4.19±0.01	0.15±0.01
3.	F3	198±1.22	44.82	3.5±0.52	4.19±0.01	0.25±0.10
4.	F4	197±0.01	48.32	2.73±0.22	4.19±0.01	0.51±0.00
5.	F5	192±1.2	45.17	2.66±0.36	4.19±0.01	0.17±0.02

Conclusion-

Irbesartan is Associate in nursing oral medication that's accustomed treat high pressure (hypertension) and diabetic renal disorder or renal disorder. By interference the action of Hypertensin, irbesartan dilates blood vessels and reduces pressure. Irbesartan is water insoluble drug, a nonpeptide angiotensin II antagonist with antihypertensive activity.

The main objective of the study is the formulation of controlled release tablet. The preformulation study of irbesartan was conducted and λmax was found at 262nm. Melting point was found at 182˚C. The standard curve of irbesartan was prepared in 0.1N HCl (λmax 262nm) and r^2 value was obtained 0.998, which are shows the linearity of absorbance and follows beer's lambert law. Organoleptic properties was determined and observed that the irbesartan is white crystalline powder, odorless, bitter in taste. Qualitative solubility study shows that the drug is practically insoluble in water and

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soluble in organic solvents. The prepared controlled matrix tablet formulation was evaluated for different parameters like Bulk density, Tapped density, Angle of repose, Carr's index, Hausner's ratio. Saturation solubility studies were carried out for pure drug, as well as for prepared controlled matrix tablet. From the result of saturation solubility studies it was observed that there was an increase in solubility of drug in tablet matrix formulation system as compared to pure drug. With increase in the concentration of carriers solubility of drug increased and the matrix tablet containing HPMC, Ethyl cellulose, pvp, magnesium stearate, lactose in tablet form has increased the solubility This improves its wettability resulting in a significant increase in solubility.

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