CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

SJIF Impact Factor: 7.187
https://doi.org/10.5281/zenodo.7629175

Available online at: http://www.iajps.com *Research Article*

FORMULATION DEVELOPMENT OF IRBESARTAN (POORLY WATER-SOLUBLE DRUG) FOR ORAL ADMINISTRATION

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Article Received: December 2022 **Accepted:** January 2023 **Published:** February 2023

Abstract:

The aim of the present study is to increase the solubility of poorly water soluble drug Irbesartan by using surfactants and formulating into immediate release tablets by using super disintegrants. Surfactants such as sodium lauryl sulfate, polysorbate, and poloxamer 800 are used for increasing the solubility of drug in water by micellisation technique. Super disintegrant such as croscarmellose sodium was used for fast disintegration. Physical properties for granules such as Bulk density, Tapped density, Hausners ratio, % compressibility, % LOD and physical characteristics for Irbesartan IR tablets such as weight variation, friability, hardness, thickness, disintegration, in-vitro dissolution were studied. % cumulative drug release of formulation T3 (having 2% Tween 80) matched with the innovator product Avapro and the similarity factor between innovator and T3 was 97.

Keywords: *Formulation, Development, Irbesartan (Poorly Water-Soluble Drug), Oral Administration*

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Please cite this article in press Gaddam Shalini et al, ***Formulation Development Of Irbesartan (Poorly Water-Soluble Drug) For Oral Administration .,*** *Indo Am. J. P. Sci, 2023; 10 (02).*

INTRODUCTION:

The active pharmaceutical ingredient in a solid dosage form must undergo dissolution before it is available for absorption from the gastrointestinal tract. For hydrophobic drugs, the dissolution process acts as the rate-controlling step and, which determines the rate and degree of absorption. Consequently, many hydrophobic drugs show erratic and incomplete absorption from the gastrointestinal tract of animals and humans. Thus, one of the major challenges to drug development today is poor solubility, as an estimated 40% of all newly developed drugs are poorly soluble or insoluble in water1 . In addition, up to 50% of orally administered drug compounds suffer from formulation problems related to their low solubility and high lipophilicity2-5 . Irbesartan (IBS), 2-butyl-3[[2-(1Htetrazole-5-yl) (1,1- biphenyl)-4yl]metyl]-1,3 diazaspiro[4,4] non-1-en-4-one antagonizes angiotensin II by blocking AT1 receptors is indicated for treatment of hypertension6 . It belongs to class II drug according to biopharmaceutical classification system (BCS) i.e. low solubility and high permeability. According to BCS drug substance is considered to be highly soluble when highest dose of drug dissolve in less than 250 mL of water. It is considered to be highly permeable when the extent of absorption in human is more than 90 % of an administered dose. Although it has excellent oral bioavailability (60-80%), but theoretically IBS exhibit solubility limited bioavailability and it would be advantageous to increase the solubility of such molecule7. Solubility of IBS was found to be increased after complexation with polymer like β-CD8.

Different methods are employed to improve the dissolution characteristics of poorly water-soluble drugs, like solubilization, pH adjustment, cosolvents, microemulsion, self-emulsification, polymeric modification, drug complexation, particle size reduction, use of a surfactant as a solubilizing agent, the pro-drug approach, and solid solutions9-10. Amongst these the most promising method for promoting dissolution is the use of the liquisolid (LS) system11-12

The objective of the present work is to perform preformulation studies to develop a portfolio of information about the Irbesartan by determining its essential physical and chemical properties like solubility, pKa, lipophilicity, solid state properties, stability drug excipient compatibility. Along with preformulation the aim of the present study was to develop Irbesartan IR tablets using different surfactants for improving the dissolution rate of Irbesartan.

METHODOLOGY:

Determination of saturation solubility:

Prior to the experimentation, water sample of Irbesartan scanned for λ max. of the drug. Taking different standard concentrations of sample plotted a standard graph. Adding excess solid (150 mg) to 100 mL deionized water placed in stoppered conical flask, pre-equilibrated to 37 ± 0.5 °C. The flasks were mechanically shaken in a shaking water bath at 100 rpm. And shake for 24 hrs. And it was filtered to get a supernatant solution. From this solution pipette out 1ml and it was diluted to 10ml with water. And the absorbance checked at 220 nm for 3 times and the average value of the absorbance was taken for calculations to get concentration of drug.

Determination of log p by shake flask method:

The partition coefficient of Irbesartan was determined in n-octanol-water systems Aqueous solution of 150mg of Irbesartan in 100 ml was prepared. To the aqueous phase 100 ml of n-octanol was added. The flasks were stoppered and agitated at room temperature for 2 h to achieve complete equilibration. The aqueous phase was analyzed by a UV apparatus for absorbance and its concentration was calculated from a preconstructed calibration curve.

Determination of pka by spectrofluorimeter:

pH measurements were made using a Radiometer PHM 84 pH meter , with a Crison 5209 combined glass electrode. An Ag/AgCl reference system was used with 3 M KCl saturated in AgCl as electrolyte. Excitation and emission spectra and relative fluorescence intensity measurements of Irbesartan solutions were obtained using a Shimadzu RF-540 spectrofluorimeter controlled by a Shimadzu DR-3 data recorder. A quartz cell of 1 cm of optic length was used. Data collection was made by means of FLUORIM software. This program allows the digital collection of the main types of scans that a commercial. Spectrofluorimeter can perform: emission, excitation and synchronic; as well as the measurement of the relative fluorescent intensity as a function of time. A Haake D8 thermostatic bath was used to keep the temperature constant, 20 + or - 0.5°C.

Drug-excipients compatibility studies:

Table 1: Ratio for the preparation drug excipient mixtures given as follows

S.NO	Name of the substance	D:E Ratio
1	Irbesartan	As such
2	Lactose Monohydrate	1:2
3	Avicel PH 101	1:2
4	Croscarmellose sodium	1:1
5	Colloidal Silicon Dioxide	1:0.25
6	Magnesium stearate	1:0.25
7	Caurnaba wax	1:1
8	Poloxamer 188	2:1
9	Sodium Lauryl Sulphate	2:1
10	Sodium Starch Glycollate	1:1
11	Starch 1500	1:5
12	Tween 80	2:1

D-Drug, E-Excipient:
Formulation:
BCS solubility study:
Weigh accurately 300mg (i.e. highest dose of Irbesartan) of Irbesartan (API) and transfer it in to 250ml of media like SGF, 0.1N HCl, 0.01N HCl, 3.0Citrate, 4.5 Acetate, 6.8 Phosphate buffer in a flask, this is subjected to 150 rpm on a mechanical shaker at 37°C for 1Hr. Then amount of the drug dissolved should be measured by using HPLC.

Prototype formulation:

Table 2: Trail Batches S1, S2, S3

S.No	Ingredients	Trial S1 (Mg/tab)	Trial S2 (Mg/tab)	Trial S3 (Mg/tab)
1.	Irbesartan	300.0	300.0	300.0
2.	LactoseMonohydrate(Pharmatose200M)	76.5	73.5	67.5
3.	Crosscarmelosesodium (Ac-di-sol)	15.0	15.0	15.0
4.	Pregelatinized Starch	90.0	90.0	90.0
5.	Sodium lauryl sulfate	3.0	6.0	12.0
6.	Aerosil 200	12.0	12.0	12.0
7.	Purified water.	q.s	q.s	q.s
	Extragranular			
1.	MCC (Avicel101)	78.0	78.0	78.0
2.	Crosscarmelosesodium (Ac-di-sol)	15.0	15.0	15.0
3.	Aerosil 200	4.5	4.5	4.5
4.	Mag Stearate	6.0	6.0	6.0
	Total Tablet Weight	**600**	**600**	**600**

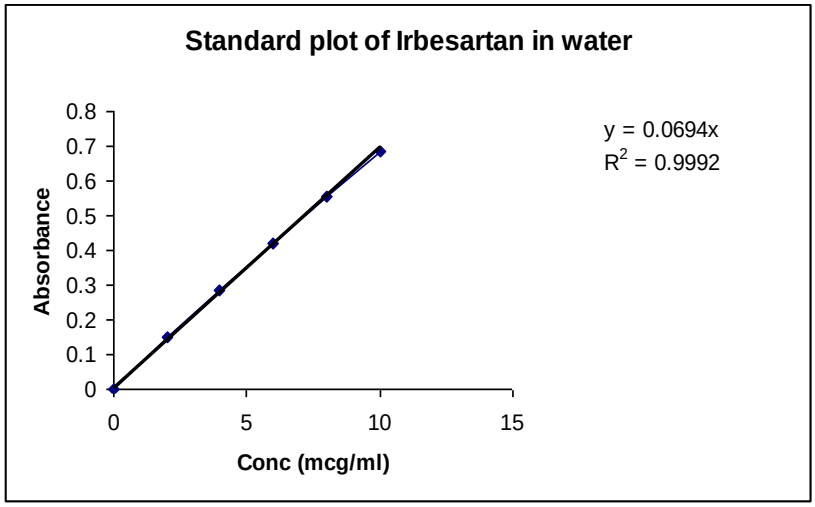
RESULTS AND DISCUSSION:

Solubility:

Solubility Study Of Irbesartan By Saturation Shake Flask Method:
Irbesartan in water was scanned for λ max (220nm)

Standard Graph of Irbesartan:
A standard graph was prepared by using solutions of 2µg/ml, 4µg/ml, 6µg/ml, 8µg/ml, 10µg/ml of Irbesartan in water at a λmax of 220nm. The UV absorbance obtained are summarized in below table

S.No	Sample concentration	Absorbance
1	2µg/ml	0.1495
2	4µg/ml	0.2835
3	6µg/ml	0.4218
4	8µg/ml	0.5565
5	10µg/ml	0.6855

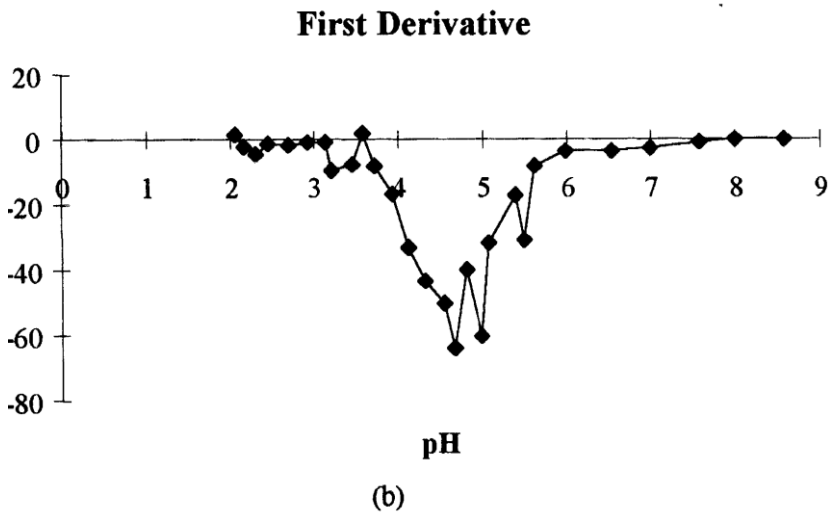


Dissociation constant of (pKa) of Irbesartan:
Observations:
Fluorescent properties of Irbesartan were carried out in order to choose the optimum wavelengths for the measurement of fluorescent intensity. The procedure consisted of an iterative process where one of the wavelengths (excitation or emission) was fixed while the other was extracted from the maximum of the spectra. That operation was made alternatively for both wavelengths to obtain the optimum values. Excitation and emission spectra were obtained at an excitation and emission slit of 5 nm width and at the highest sensitivity of the instrument. Optimal wavelengths are collected and shown in below:
Optimized values of the excitation and emission wavelengths:
Excitation wavelength (nm) = 259nm.
Emission wavelength (nm) = 385nm.
Solutions of Irbesartan at different pH values were prepared to study the influence of pH on relative fluorescent intensity, I F, rel (Relative fluorescent intensity)

The plot of I F, rel (Relative fluorescent intensity) – pH showed decreasing sigmoidal curve.
a). Relative fluorescent intensity (IF,rel)-pH data at 0.5 M ionic strength for Irbesartan.

In this work, graphical (derivatives and curve fitting) and numerical (LETAGROP SPEFO) methods, normally used for the determination of pKa values from A–pH data, will be applied. From the curves obtained in the IF,rel–pH plots for Irbesartan, the existence of a unique acid–base equilibrium in the pH range 2–9 can be deduced.
After getting the plot of relative fluorescent intensity versus pH data. pKa values were obtained from the maximum–minimum points for the first derivative and from the intersection of the function with the abscissa axis for the second derivative. Rough pKa values were calculated from these representations.

The curve-fitting method with a normalized variable was applied to the IF,rel–pH data o for the Irbesartan using ApH software , designed for the determination of pKa values from A–pH data.



(b)

Table 4: BCS Solubility Study of Irbesartan

S.No	Media	Mg/250ml	Mg/900ml
1	SGF	297.34	1070.64
2	0.1N HCl	307.7	1107.73
3	0.01N HCl	98.58	354.9
4	3.0Citrate	41.85	150.64
5	4.5Acetate	26.09	93.91
6	6.8Phosphate	212.22	764

SGF- Simulated gastric fluid

Table 5: Physical characteristics of granules

Trial No.	%LOD	Bulk density (gm/cm^2)	Tapped density (gm/cm^2)	% Compressibility	Hausner Ratio
S1	1.56	0.487	0.665	26.82	1.367
S2	1.64	0.469	0.631	25.58	1.34
S3	1.46	0.5	0.645	22.5	1.270
P1	1.71	0.444	0.588	24.44	1.323
P2	1.52	0.486	0.667	23.99	1.364
P3	1.62	0.443	0.588	24.42	1.322
T1	1.47	0.469	0.631	25.58	1.34
T2	1.74	0.51	0.643	22.4	1.268
T3	1.65	0.485	0.667	23.98	1.363

Table 6: Evaluation of Irbesartan IR Tablets

Trial	Weight variation (mg)	Friability (%)	Hardness (Newton's)	Thickness (mm)	Disintegration (min)
S1	602±2.35	0.14	110 - 120	7.2±0.1	7.30
S2	601±2.04	0.12	110 - 120	7.1±0.1	7.27
S3	603±2.03	0.17	110 - 120	7.2±0.1	7.29
P1	602±2.06	0.2	110 – 120	7.3±0.1	2.40
P2	604±2.41	0.24	110 - 120	7.1±0.1	2.36
P3	602±2.13	0.26	110 - 120	7.1±0.1	2.24
T1	601±2.35	0.23	110 - 120	7.2±0.1	2.14
T2	604±2.15	0.24	110 - 120	7.2±0.1	2.02
T3	602±2.38	0.28	110 - 120	7.2±0.1	1.50

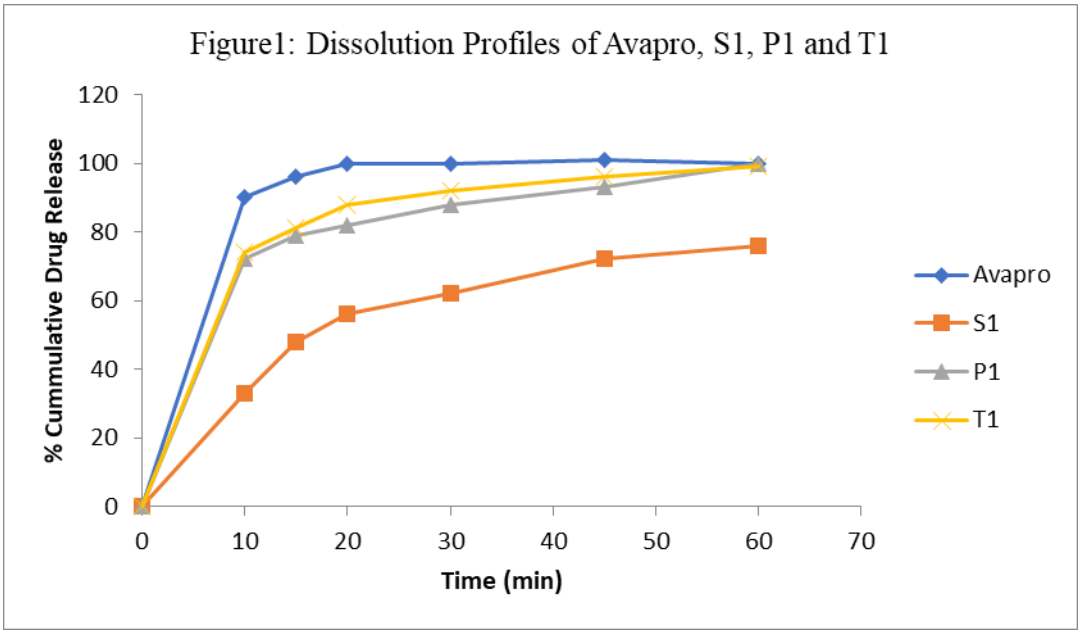


Table 7: Comparing dissolution profiles of innovator and trial S2, P2 and T2

% Cumulative drug release				
Time (Min)	Avapro	S2	P2	T2
10	90±2.01	33±1.26	81±2.38	86±1.39
15	96±1.98	48±1.64	85±2.08	89±1.97
20	100±2.37	56±1.94	89±2.61	94±1.64
30	100±2.46	62±2.08	95±2.91	99±2.08
45	101±1.56	74±2.18	100±1.43	100±1.34
60	100±2.68	95±2.64	99±2.42	99±2.58

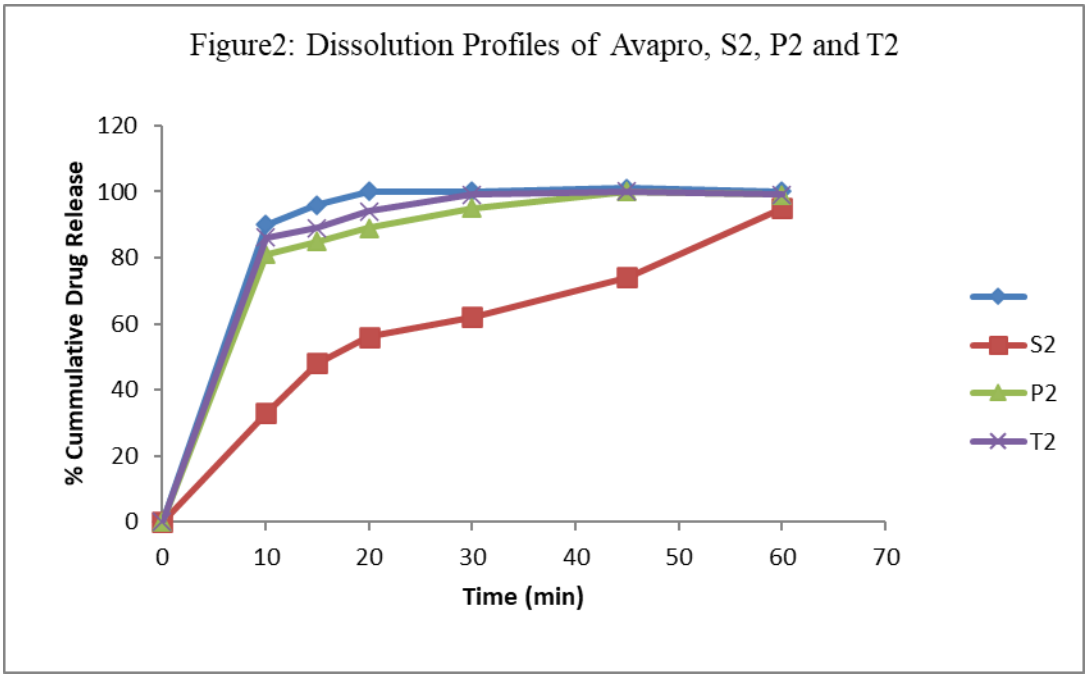
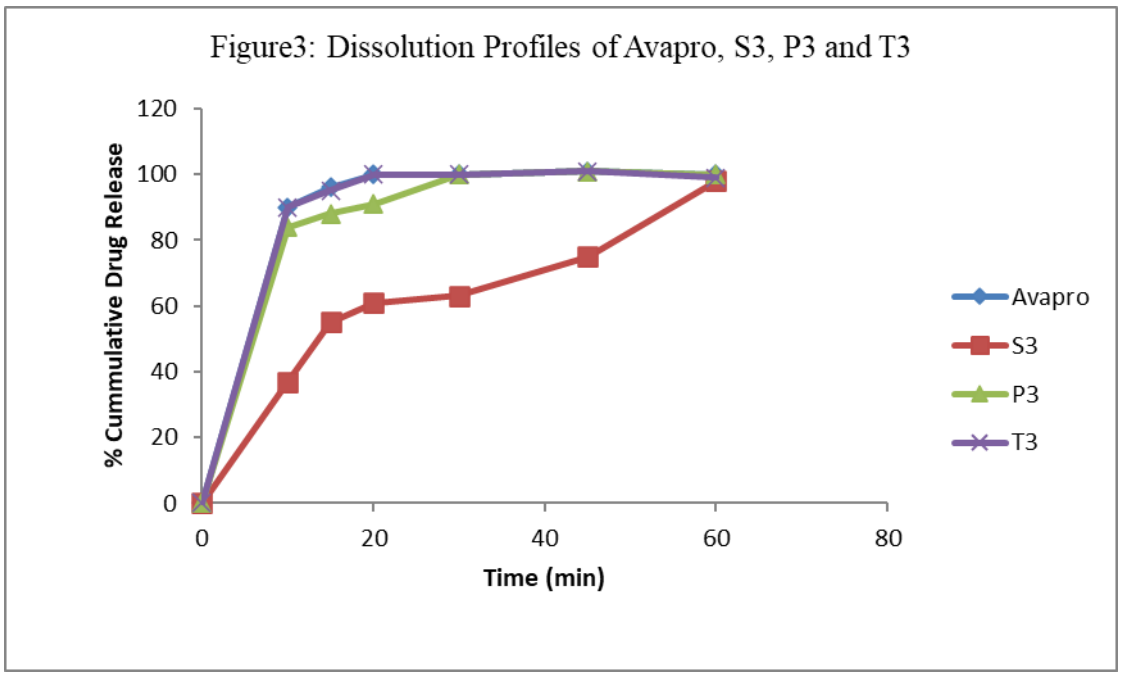


Table 8: Comparing dissolution profiles of innovator and trial S3, P3 and T3

% Cumulative drug release				
Time (Min)	**Avapro**	**S3**	**P3**	**T3**
10	90±2.01	37±3.15	84±1.96	90±3.48
15	96±1.98	55±3.79	88±1.46	95±3.62
20	100±2.37	61±2.96	91±1.91	100±2.43
30	100±2.46	63±3.68	100±2.16	100±2.19
45	101±1.56	75±2.76	101±2.34	101±1.58
60	100±2.68	98±2.16	100±2.61	99±1.64



Similarity Factor of Different Formulations:

The similarity factor (f2) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent dissolution between the two curves.

Table 9: Similarity Factor of Different Formulations

S.NO.	Trial Batch	f2
1	S1	19.1
2	P1	42.9
3	T1	48
4	S2	20
5	P2	56
6	T2	68.4
7	S3	22
8	P3	63
9	T3	97

The similarity factor between formulation T3 and innovator product found to be 97

CONCLUSION:

Irbesartan has solubility and dissolution limited bioavailability. Hence the liquisolid technique was chosen to enhance the dissolution properties of IBS. The IBS liquisolid tablets were prepared using Avicel PH 102 and Cab-O-Sil M5 as a carrier and coating materials. It showed significant increase in dissolution as compared to DC tablets. There is a relationship between the powder excipient ratio and the in-vitro release of IBS from liquisolid tablets having the same liquid load factor. The powder excipient ratio was directly proportional to the in vitro release of IBS from their formulations. In conclusion, Liquisolid tablet of IBS which can be scaled-up industrially is promising approach for enhancing solubility and dissolution rate.

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