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In-depth Exploration of the Pharmacological, Analytical, and Pharmaceutical Attributes of Irbesartan

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Irbesartan, an angiotensin II receptor blocker (ARB), has gained prominence in the management of hypertension and diabetic nephropathy due to its potent antihypertensive and Reno protective effects. This review provides a comprehensive overview of the pharmacological, analytical, and pharmaceutical characteristics of Irbesartan. Pharmacologically, Irbesartan selectively antagonizes the angiotensin II type 1 (AT1) receptors, leading to vasodilation, reduced aldosterone secretion, and consequently blood pressure lowering. The drug also exhibits favourable effects on renal function, making it a cornerstone therapy for diabetic nephropathy. Analytically, various

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chromatographic methods including high-performance liquid chromatography (HPLC) and Ultra-performance liquid chromatography (UPLC) have been developed and validated for the quantification of Irbesartan in biological samples and pharmaceutical formulations, owing to its importance in pharmacokinetic studies and quality control processes. Moreover, spectroscopic techniques such as UV-visible spectrophotometry have been utilized for Irbesartan determination due to their simplicity and cost-effectiveness. Pharmaceutical considerations encompass formulation strategies, stability studies, and bioavailability enhancement techniques aimed at ensuring the efficacy and safety of Irbesartan formulations. The regulatory approval of Irbesartan-containing products by major health authorities underscores its clinical significance and quality assurance.

Keywords: Irbesartan; angiotensin II receptor blocker; HPLC; UPLC; bioavailability.

1. INTRODUCTION

Irbesartan is a drug used to treat high blood pressure, heart failure, and diabetic renal disease. It is marketed under several trade names, including Avapro. It makes sense to start treating high blood pressure with it. It is consumed orally. Some version combines hydrochlorothiazide and irbesartan. Patented in 1990, irbesartan received medical approval in 1997. It can be purchased as a generic drug. With over 3 million prescriptions, it ranked as the 172nd most frequently prescribed drug in the US in 2021 [1]. Angiotensin II receptor blocker (ARB) is irbesartan. It functions by obstructing an internal chemical that tightens blood arteries. Irbesartan causes the blood vessels to relax as a result. This increases the amount of blood and oxygen that the heart receives while lowering blood pressure [2]. Adults and children who are at least 6 years old with hypertension (high blood pressure) can be treated with irbesartan. Blood pressure reduction may lessen your chance of having a heart attack or stroke. Irbesartan is also used to treat kidney problems caused by type 2 diabetes [3].

1.1 Chemical Structure [4]

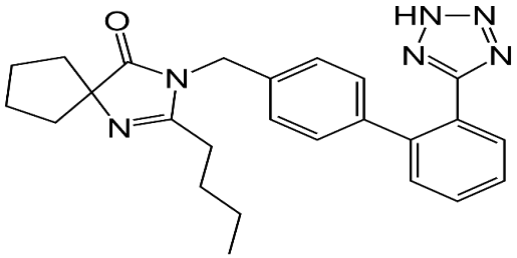

Fig. 1. Chemical structure of Irbesartan

Table 1. Drug profile [5]

Drug	Irbesartan
IUPAC name	2-butyl-3-[[4-[2-(2*H*-tetrazole-5-yl) phenyl] phenyl] methyl]-1,3-diazaspiro [4.4] non-1-en-4-one
Chemical formula	$C_{25}H_{28}N_6O$
Molecular weight	428.5 g/mol
Boiling point	648.6
Melting point	180-181 °C
Physical state	Solid
Solubility	Practically insoluble in water Slightly soluble in alcohol, methylene chloride
Log P	4.5
Color	White
t 1/2	11 to 15 hours

Table 2. Chemical taxonomy [6]

Description	This compound belongs to the class of organic compounds known as biphenyls and derivatives. These are organic compounds containing benzene rings linked together by a C-C bond.
Kingdom	Organic compounds
Superclass	Benzenoids
Class	Benzene and substituted derivatives
Subclass	Biphenyls and derivatives
Direct Parent	Biphenyls and derivatives
Alternative parents	Phenyl tetrazoles and derivatives / Alpha amino acids and derivatives / Imidazolinones / Heteroaromatic compounds / Propargyl-type 1,3-dipolar organic compounds / Carboximidamides / Carboxamidines / Azacyclic compounds / Organopnictogen compounds / Organic oxides
Substituents	2-imidazoline / Alpha-amino acid or derivatives / Amidine / Aromatic hetero polycyclic compound / Azacycle / Azole / Biphenyl / Carbonyl group / Carboximidamide / Carboxylic acid amidine
Molecular framework	Aromatic hetero polycyclic compounds

1.2 Pharmacology

Pharmacodynamic [7]: Angiotensin receptor blockers like irbesartan are used to treat diabetic nephropathy and hypertension. Its broad therapeutic index allows for doses as low as 150 mg per day, while 900 mg per day was well tolerated in healthy human subjects. Its lengthy duration of action stems from the fact that it is often given once daily.

1.3 Pharmacokinetics [8]

Absorption: The bioavailability of irbesartan remains unaffected when consumed with meals.In one trial, irbesartan dosages of 150 mg, 300 mg, 600 mg, and 900 mg were administered orally to healthy participants either once or more. Irbesartan has a T_{max} of 1.5–2 hours and is 60–80% bioavailable.

Distribution: Irbesartan is given in a volume of 53–93 L. 90% of the drug in plasma is linked to proteins, primarily albumin and α1-acid glycoprotein.

Metabolism: The liver uses glucuronidation and oxidation to metabolize irbesartan primarily. With CYP3A4 playing a very little role, CYP2C9 is primarily responsible for metabolism. The metabolic process of irbesartan also involves some hydroxylation. Irbesartan can be oxidized to the M3 metabolite, hydroxylated by CYP2C9 to one of the M4, M5, or M7 metabolites, or glucuronidated by UGT1A3 to the M8 metabolite. The M1 metabolite, which is subsequently oxidized to create the M2 metabolite, is formed by the hydroxylation of the M4, M5, and M7 metabolites. Before being hydroxylated to become the M2 metabolite, the M4 metabolite may potentially be oxidized to the M6 metabolite. Ultimately, irbesartan produces the small metabolite SR 49498 by an unidentified process.

Elimination: Urine contains 20% of the radiolabeled oral dosage of irbesartan, whereas feces contain the remaining portion. Less than 2% of the dosage is found as a substance unaltered in urine. Irbesartan has a terminal elimination half-life of 11–15 hours.

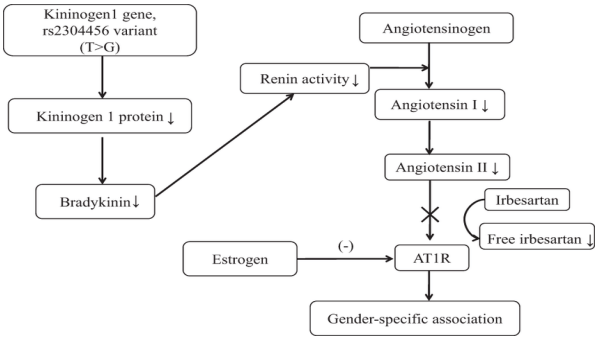

Fig. 2. Mechanism of action of Irbesartan

Table 3. List of available marketed brand name of irbesartan [19]

S. No.	Trade Name	Company Name	Formulation	Dosage strength (mg/tablet)
1	Avapro	Bristol-Myers Squibb pharmaceutical	Tablet	75,150,300
2	Approval	Sanofi	Tablet, Film-coated	75,150,300
3	Irovel	Sun Pharmaceutical Industries Ltd.	Tablet	75,150,300
4	Irbesartan sanndoz	Sandoz pharmaceutical	Tablet	75,150,300
5	Karvea	Aspen pharmacare	Tablet	75,150,300
6	Irbesartan teva	Tev pharmaceuticals	Tablet	75,150,300
7	Irbesartan zentiva	Zentiva pharmaceutical	Tablet	75,150,300
8	Irbesartan accord	Accord Healthcare	Tablet	75,150,300
9	Irbesartan arrow	Arrow generiques pharmaceutical	Tablet	75,150,300
10	Coaprovel	Sanofi pharmaceutical	Tablet	75,300

Table 4. List of HPLC methods for the quantification of Irbesartan [10-21]

S. No	Column type	Mobile phase	Run time (min)	RT (min)	Flow Rate (ml/min)	Wave length (nm)	Linearity range (µg/ml)	LOD (µg/ml)	LOQ (µg/ml)	Correlation coefficient
1	LC-10 AT	Methanol, water [90:10 v/v]	----	----	1	230	5-25	0.83	2.78	0.9965
2	Raptor C-18, 100 mm x 4.6 mm id; 5 µm)	Ammonium acetate buffer-acetonitrile 60:40 v/v	10	2.96	1.0	230	1-12	0.103	0.345	>0.99
3	Phenomenex column-18 (250 x 4.mm,5 µm**)**	Phosphate buffer-methanol 60:40 vol	6	2.346	1.0	230	75-225	1.173	3.911	0.9993
4	Cosmosil C18, 4.6 ID X 250mm 5µ	Methanol, water 80;20vol	7.04	3.30	1.0	400-200	60-100	0.710	0.116	0.998
5	Water-bridge C18 column (5 µm, 25 x 0**.**46 cm)	Acetonitrile, orthophosphoric acid	**----**	6.18	1	240	5-30	0.06	0.05	0.9973
6	ACE RP-C18 column (250 mm x 4.6 mm, 5µm)	Potassium Dihydrogen Phosphate, acetonitrile 80:20%	**----**	**----**	1.5	220	30-180	0.14	0.44	1.0
7	RP-18e column (100 mm x 4.6 mm i.d.)	Phosphate buffer, Acetonitrile.50:50, V/V	3	2.23	1.0	270	10-200	2.34	7.70	R>0.9997
8	Phenomenex C18 column (25 cm x 0.46 cm, 5µ)	Phosphate buffer, Acetonitrile 55:45% v/v	15	11.376	1.0	224	----	----	----	0.997
9	C18 column (250x4.6) mm	Acetonitrile, Phosphate buffer 40:60 v/v	---	15.52	1.5	254	------	0.1	0.34	**----**
10	C 18 column (75 mm x 4.6 mm; 3.5 µ)	Ammonia Acetate Buffer-Acetonitrile 40:60 v/v	7.5	1.20	1-3.5	220	0-4.5	0.189	0.630	0.999
11	Supelcosil C18 column (150 mm x 4.6 mm, 5 µm particle size)	Methanol-Tetrahydrofuran-Acetate buffer 47:10:43 v/v/v	>6	----	0.75	271	0.08-0.4	0.02	0.06	0.9976
12	Inertsil ODS C18 column (5µm column having 250 x 4.6 mm)	Methanol-Acetonitrile and 2% OPA [40:40:20% v/v/v]	6	4.5	1.5	260	10-70	10	30	0.9982

Table 5. List of LC-MS methods for the quantification of Irbesartan [21-29]

S. No	M/Z Value	Capillary temperature (^{0} C)	Ionization voltage (V)	Column type	Solvent mixture	Mass spectroscopy used	RT (min)	Retention time (min)
1	429.3-195.1	-550	-5500v	POLAR-RP80A	0.1% formic acid, 100% methanol.	API 3000	4	2.75
2	**----**	ambient	**----**	C-18[150x4.6mm, 5 µm]	Buffer {potassium Dihydrogen Orthophosphate PH:3.5}, methanol, Acetonitrile.	**----**	**10**	**3.35**
3	427.1-206.9	40	-3500	C18[100mmX4.6mm,5 µm]	Methanol 0.1% Formic acid	ESI [tandem]	3.5	2.20
4		40	**----**	C18 [250x4.6mm,5mm	Acetonitrile, methanol	**----**	**----**	**6.3**
5	492.1-206.9	-80	----	C18 [4.6x100mm,3.5 µm	Ammonium Formate	Tandem mass spectroscopy	15.00	12.40+0.06
6	427.1-192.9	550	-4200	RP-18e [50-4.6 mm]	Acetonitrile, ammonium Formate solution	API3000 triple quadrupole	3	1.2
7	---	25	----	C18 column [150x4.6mm,5 µm]	Phosphate Buffer, Acetonitrile	----	6	2.72
8	429 m+1 427m-1	250	4.5kv	XR-ODS 50x3.0mm,2.2µ m	Formic Acid, acetonitrile	Triple quadrupole	----	7.663

Table 6. List of UV methods for the estimation of Irbesartan [30-36]

S. No.	Wavelength (nm)	Linearity range (µg/ml)	LOD (µg/ml)	LOQ (µg/ml)	Correlation coefficient
1	225-230	2-20	3.3	10	0.999
2	232	10-18	0.3	1	0.998
3	263	10-100	0.07815	0.23681	0.999
4	237.8&247.8	10.0-50.0	1.14	1.63	0.9991
5	263.4&281	5-15	0.6374	1.9314	0.9991
6	226.00	5-3	0.033	0.1008	0.999
7	246	5-4	**---**	----	0.999

Toxicity: In humans, the oral TDLO is 30 mg/kg/6 W. Overdosing can cause bradycardia or tachycardia as well as hypotension. If traditional vasopressors are unable to maintain blood pressure management, terlipressin may be used to treat hypotension and tachycardia.

Mechanism of action [37]: Angiotensin II cannot bind to the AT1 receptor in tissues such as the adrenal gland and vascular smooth muscle when irbesartan is taken. The AT1 receptor is bonded to by irbesartan and its active metabolite with an 8500-fold higher affinity than the AT2 receptor. Because irbesartan inhibits angiotensin II binding, blood pressure is lowered by relaxing the vascular smooth muscle and preventing aldosterone release.

Otherwise, angiotensin II would bind to the AT1 receptor, causing vasoconstriction and the release of aldosterone, which would increase blood pressure.

2. CONCLUSION

In conclusion, a deep understanding of the pharmacological actions, analytical methods, and pharmaceutical aspects of Irbesartan is crucial for optimizing its therapeutic utility and ensuring patient care in various clinical settings.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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