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APPLICATION OF MIXED HYDROTROPY FOR THE SOLUBILITY ENHANCEMENT OF IRBESARTAN

GAWANDAR P*, BIYANI KR[2], KHEDEKAR S[1, 3] AND KHEDEKAR J[4]

1: Assistant Professor, Anuradha College of Pharmacy, Chikhli. Dist. Buldana, India

2: Principal, Anuradha College of Pharmacy, Chikhli. Dist. Buldana, India

3: Assistant professor, Anuradha College of Pharmacy, Chikhli. Dist. Buldana, India

4: Assistant professor, Anuradha College of Pharmacy, Chikhli. Dist. Buldana India

***Corresponding Author: Dr. Pooja Gawandar: E Mail: poojagawandersaj@gmail.com**

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ABSTRACT

Bioavailability of Irbesartan (IRB) is only 60% due to its poor aqueous solubility and dissolution rate. Irbesartan (IRB) is an angiotensin II receptor antagonist used in the treatment of hypertension. It delay progression of diabetic nephropathy and also indicated for the reduction of renal disease progression in patients with type II diabetes, hypertension and micro albumin urea or protein urea. According to BCS classification IRB belongs to class II. The aim for present paper to increased the Solubility of IRB by hydrotropic solid dispersion technique which is supposed to improve oral bioavailability. Mixed hydrotropic solid dispersions of IRB were prepared using various hydrotropic agents (Sodium Salicylate, Urea, Niacimide, Sodium Citrate and Sodium alginate) in different ratios. The dissolvability of chose plans was assessed after a preliminary of actual solvency investigation of all the Solid scattering. The examination has been made by evaluating the dissolvability of a medication in the individual hydrotropic specialist and afterward with blends of a hydrotropic specialist. Different hydrotropic specialists were utilized separately in fluctuating convergences of 5%w/v to 40%w/v. The shake cup strategy was utilized to portray the dissolvability of medication pre and post-blended Hydrotropy application. The strong scattering is ready by dissolvable dissipation method. Strong scattering has been portrayed by an instrumental concentrate like XRD (D8 Advanced model of Brukar Axs Company in the 30-800 2 Theta scale) FTIR Shimadzu (IR Prestige 21). The outcomes so acquired were characteristic of dissolvability

upgrade of Irbesartan in the mix of a hydrotropic mix than that of individual hydrotropic specialist focus. Hydrotropic solubilization of ineffectively solvent medications utilizing non-micelle-creating substances is a compelling, non-poisonous and green innovation.

Keywords: Bioavailability, Mixed hydrotropy, Solubility enhancement, Irbesartan

INTRODUCTION

Solubility is the rate-limiting step in the dissolution of the drug. Poor aqueous solubility cultivates the challenge in the design and development of dosage form. The drug to be ingested orally should have sufficient aqueous solubility to achieve desired bioavailability.[1] Hydrotherapy is the effective solubility enhancement method where aqueous solubility of poorly water-soluble drugs is increased by co-dissolving drugs with extremely water-soluble inert compounds, also known as hydrotropic agents. Mixtures of hydrotropic agents further increase the solubility of poorly water-soluble substances due to the synergistic additive effect of the solubilizers. [2-4] Solid dispersion is a group of solid products consisting of at least two different components, generally hydrotropic matrix and hydrophobic drug.[5] The concept of mixed hydrotropic solid dispersion is novel, safe, and cost-effective for enhancing solubility and bioavailability of poorly water-soluble drugs by dissolving drugs in non-ionized form.[6] Irbesartan is an orally active antihypertensive drug that belongs to BCS class II category.[7,8] The objective of this study was to improve the solubility of Irbesartan using hydrotropic solid dispersion by use of hydrotropic combination so that oral bioavailability can be increased.

Strong scattering innovation is the study of scattering at least one dynamic fixings in an inactive framework in the strong state to accomplish an expanded disintegration rate, further developed solvency and steadiness. On account of scattering, the expanded disintegration rate in the gastrointestinal parcel may not be accomplished in light of the reconversion of salts into totals of their individual corrosive (or) base structures. solubilization of medications in natural solvents or in fluid media by the utilization of surfactants and co-solvents prompts fluid details that are normally unfortunate from patient worthiness and commercialization. Strong scattering might be acquired in various strategies however there are two techniques that are broadly utilized e. g. dissolvable strategy and combination technique. [8,10]

MATERIALS AND METHODS

Materials:

The Irbesartan was obtained from CTX Life science Pvt. Ltd, Surat. Sodium citrate, Sodium Salicylate, Urea, Sodium benzoate, and all other chemical and solvents were of analytical grade and freshly prepared water was used throughout the study

Method:

It is a relatively new technique in which the drug and selected hydrotropic agent are used to prepare a hydrotropic blend in different ratio in, distilled water is added at a temperature ranging between 80-85°C. Then the selected hydrotropic agent are taken and added to water. Then add drug slowly to the beaker and Teflon coated magnetic bead is dropped in beaker, temperature is to be maintained for optimum stirring and stirring is continued until maximum loss of water to form semisolid mass. This semisolid mass is spread on several watch glasses and is placed in oven maintaining a temperature of 60-65°C. Then allow the semisolid mass for drying pass it through sieve no.100 and kept in desiccators for 6 days. [17] **Figure 1.1** show the technique.

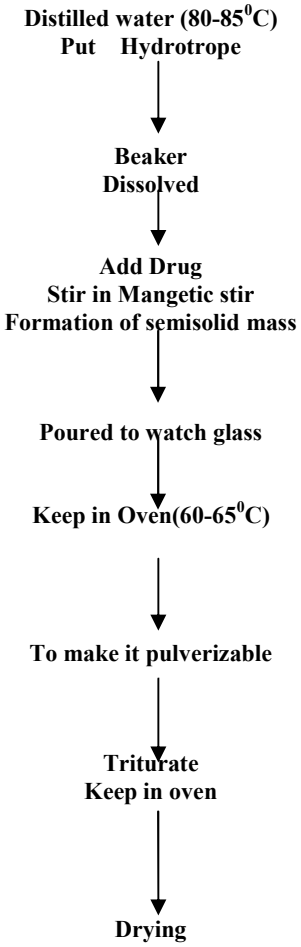

Figure 1.1 - Preparation of hydrotropic solid dispersion

Determination of solubility

Drug saturation solubility was determined in distilled water by the shake flask method. An excess quantity of drug (Irbesartan) was added to 10ml distilled water, then it was shaken at a speed of 200rpm with a mechanical shaker for 24hrs, at room temperature. The solution was centrifuged and absorbance was recorded at 250nm using a UV-visible spectrophotometer (schimadzuUV2600)[8,12] solubility was calculated based on the observations.

Equilibrium solubility studies in different hydrotropic agents[14-19] The solutions of Hydrotropic agents like Sodium Salicylate (SS), sodium Citrate (SC), sodium acetate (SA), and Urea (U) i.e. 5%, 10%, 20%, 30%, 40% w/v were prepared in distilled water. Saturated solutions of the drug were prepared in individual hydrotropic agent solutions and placed in a vial. To achieve equilibrium solubility of Irbesartan in hydrotropic agent solution, each vial was shaken on a mechanical shaker for 12hrs. The arrangement of the hydrotropic mix was permitted to equilibrate for 24hrs following centrifugation at 2000 rpm for 10min in ultra-rotator and further sifted through grade 41filter paper. Aliquots were appropriately weakened with refined water and examined utilizing a UV spectrophotometer at 250 nm. Dissolvability upgrade proportion (SER) insolubility was determined by looking at the solvency of Irbesartan in refined water and hydrotrope arrangement. The noticed aftereffects of dissolvability upgrade of Irbesartan in individual hydrotrope are recorded in **Tables 1 and 2**.

Equilibrium Solubility study in mixed hydrotropic agent [13, 12]

The equilibrium solubility study methodology was repeated by replacing individual concentrations of the hydrotropic agent with the combination of two or more hydrotropic agents. The mixed hydrotropic blend combinations so prepared were having different concentration ratios of hydrotropic agents dissolved in water to have a clear solution. It denoted by A (Sodium Salicylate), B(Sodium benzoate), C (Urea), D (Sodium Citrate). The saturated concentration of the drug was added to the mixed hydrotropic agent solution and mechanically shaken on a magnetic stirrer at RT for 12h. The obtained results are shown in **Table 3**. The concentration of 5% to 40 % hydrotropic agents combinations were prepared and studied the solubility enhancement method.

Table 1: Screening of 10% concentration of hydrotropic agent

Sr. No.	Hydrotropic agent	Solubility (mcg)
	Water	170
1	Sodium acetate	192
2	Sodium benzoate	186
4	Urea	193
5	Niacimide	116
6	Citric acid	185
7	Sodium citrate	205
8	Sodium Salicylate	198
9	Ibuprofen	190
10	PEG-400	165
11	Sodium saccharine	188

Table 2: Screening of 40% concentration of hydrotropic agent

Sr. No.	Hydrotropic agent	Solubility (mcg)
	Water	170
1	Sodium acetate	190
2	Sodium benzoate	203
4	Urea	193
5	Niacimide	165
6	Citric acid	195
7	Sodium citrate	224
8	Sodium Salicylate	204
9	Ibuprofen	198
10	PEG-400	166
11	Sodium saccharine	182

Table 3: Equilibrium solubility of Irbesartan in mixed hydrotropic blends

Sr. No.	Hydrotropic Blend	Final conc. (%w/v)	Ratio
1(A)	A+B+C+D	40	5:10:10:5
2(B)	A+B+C+D	40	5:10:5:10
3(C)	A+B+C+D	40	10:5:10:5
4(D)	A+B+C+D	40	10:5:5:5
5(E)	A+B+C+D	40	10:10:5:0
6(F)	A+B+C+D	40	0:10:10:10
7(G)	A+B+C+D	40	0:10:10:10
8(H)	A+B+C+D	40	10:10:10:0
9(I)	A+B+C+D	40	0:15:0:15
10(J)	A+B+C+D	40	15:0:15:0
11(K)	A+B+C+D	40	0:15:15:0
12(L)	A+B+C+D	40	0:0:15:15
13(M)	A+B+C+D	40	0:15:15:0
14(N)	A+B+C+D	40	15:0:0:15

Formulation of hydrotropic solid dispersion of Irbesartan [14, 17]

For the planning of hydrotropic strong scattering, 1.5 gm Sodium Salicylate, 1.5 gm Sodium Citrate, 0.5 gm of Urea, 0.5 gm sodium acetic acid derivation was weighed precisely and blended appropriately. Further, a little amount of refined water adequate to break up the above hydrotropic mix was added. The disintegration of the hydrotropic mix was worked with by fomentation with a Teflon-covered attractive rice dot on a fast attractive stirrer. After complete disintegration of an above hydrotropic mix, 1 g of Irbesartan (a medication to transporter proportion was1:4) was broken down in the above arrangement, and the temperature was kept up within the scope of 55-60°C to work with the water vanishing. The revolution speed in the shake carafe technique utilizing

rice attractive dot consequently changes with an adjustment of the extent of water in the scattering. The strong scattering consequently acquired was dried utilizing a hot air broiler to vanish any dampness entangled in the scattering and no further weight reduction could be achieved. The dried mass is then pulverized with a glass mortar pestle and uniform molecule size was achieved by passing the ground up mass through strainer number 60.

Evaluation of hydrotropic Solid dispersion of Irbesartan

The hydrotropic solid dispersion so prepared by mixed hydrotropy method was evaluated with the characteristic parameters as like pure drug Irbesartan. The drug assay was performed in addition by dissolving solid dispersion equivalent to 10 mg drug in100ml phosphate buffer pH 6.8. After suitable dilution, the absorbance was measured at 250nm. The drug content of Irbesartan was calculated using the calibration curve. [21]

RESULTS AND DISCUSSION

Saturated solubility study of Irbesartan in distilled water

The Saturated solubility of Irbesartan was determined in distilled water and it was found to be 0.029µg/mL. According to the BCS classification system, the solubility of a drug in distilled water is below the significant solubility value and hence the drug is said to be poorly water-soluble.

Equilibrium solubility studies in different hydrotropic agents

The shake flask method was employed to determine the equilibrium solubility of Irbesartan in individual hydrotropic agent solutions. The values so obtained are mentioned in **Table 4**. A significant variation has been observed in both solubility values of Irbesartan. The change in solubility is concluded as the result of the hydrotropic agent solution.

Equilibrium solubility of Irbesartan in mixed hydrotropic blends

Mixed Hydrotropy blends of hydrotropic agents were prepared as per the hydrotropic combination given in **Table 3**. Solubility of Irbesartan was determined in mixed hydrotropic blends and results are reported in **Table 4**. Out of the 10 hydrotropic agent solutions, the lowest solubility of the drug was found in Niacimide solution. So, Niacimide has not been considered for combination. The remaining hydrotropic agents were selected for mixed hydrotropic blend. About three hundred and eighty four times enhancement in solubility of Irbesartan was observed in the mixed hydrotropic blend having 0:15:0:15 concentration ratio of sodium benzoate: sodium citrate.

X-ray powder diffraction analysis of Irbesartan

X-beam diffraction designs express that unadulterated Irbesartan was in a glass-like state, as it showed sharp particular pinnacles prominently at 2θ diffraction points of 4.75o, 12.49o, 19.45o, 23.18o. PEG4000 was translucent in nature and gives two trademark tops, one at 19.2° and the other more extensive one at 23.43o. The reflections (explicit pinnacles) relating to the medication and other excipients were found in the plan diffractogram with diminished force when contrasted with the drug alone. Displayed in **Figure 1.2**.

Characteristics' peaks of Irbesartan **(Figure 1.2)** were absent in the diffractogram of solid dispersion of Irbesartan which conclude miscibility of Irbesartan in hydrotropic agent. From the diffractogram of solid dispersion, it also concludes that Irbesartan was converted from crystalline to amorphous form.

FTIR Spectrophotometric study

The Mixed hydrotropic solid dispersions were characterized by FTIR using Shimadzu 8400S. The spectra have shown the same characteristic bands as in pure drugs. No additional peaks were observed in the spectra concluding that there is no interaction between hydrotropic agents and drugs. The obtained spectra of the sample are shown in **Figure 1.4** and the interpretation is given in **Table 5**.

Drug content/Assay Drug content assay of hydrotropic solid dispersion of drug i.e. Irbesartan was found to be 97.0%. It indicates that the drug is uniformly dispersed in hydrotropic solid dispersion and net loss has been significantly controlled.

Table 4: Equilibrium solubility of Irbesartan in mixed hydrotropic blends

Sr. No.	Hydrotropic Blend	Absorbance at 280 nm	Concentration (in mcg/ml)	Solubility Enhancement Ratio
1	A	0.555	37.818	298
2	B	0.366	25.65	202
3	C	0.384	26.81	211.69
4	D	0.251	18.32	144.7
5	E	0.282	20.52	161.89
6	F	0.612	41.46	327.38
7	G	0.637	43.091	340.19
8	H	0.45	31.07	245.28
9	I	0.725	48.734	384.74
10	J	0.544	37.104	292.92
11	K	0.592	40.61	317.06
12	L	0.517	35.38	279.37
13	M	0.5070	34.714	274.05
14	N	0.389	27.14	214.29

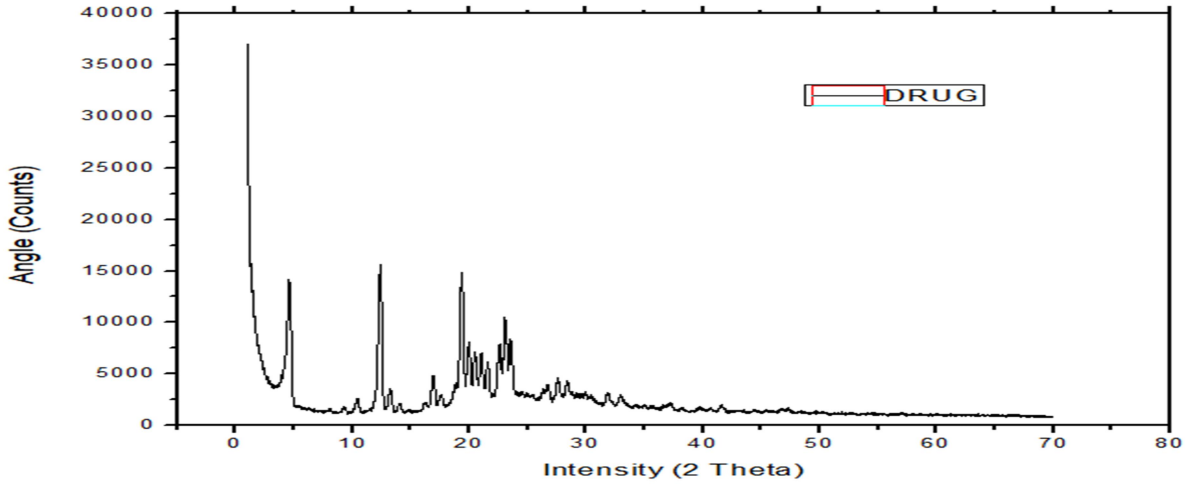

Figure 1.2: XRD of Irbesartan

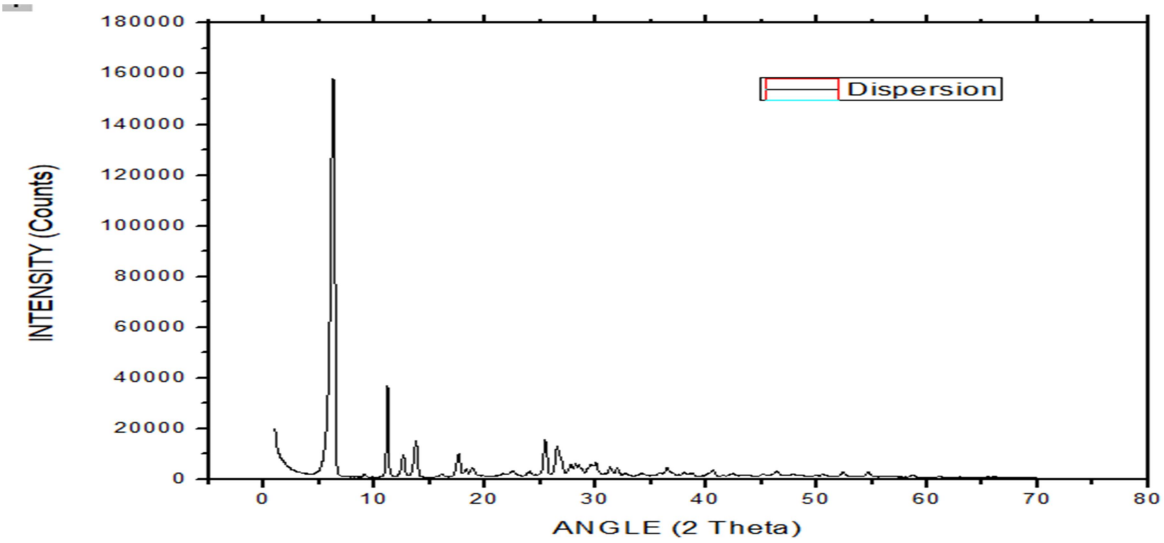

Figure 1.3: XRD of Irbesartan (IRB) solid dispersion

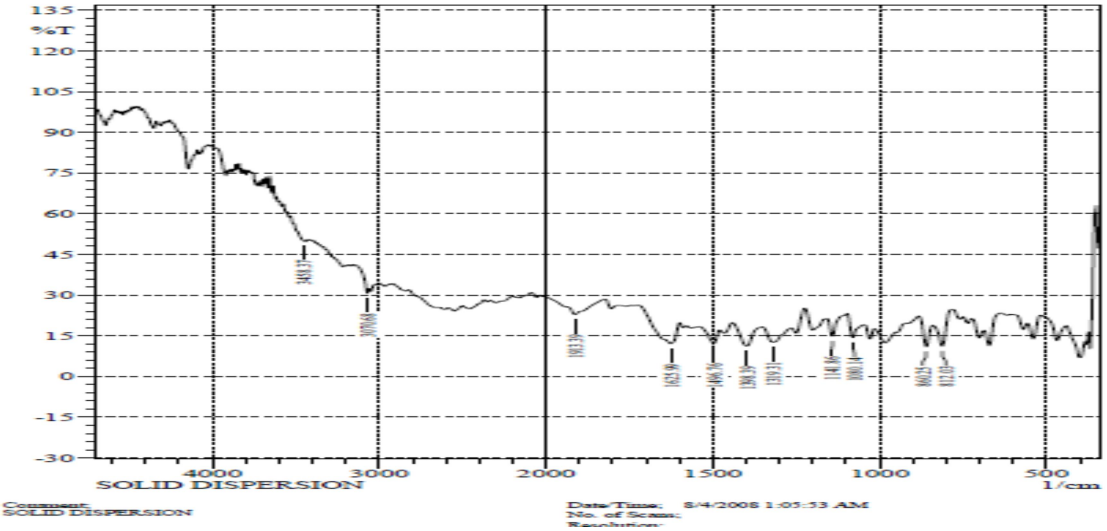

Figure 1.5 - FTIR spectra of IRB Solid dispersion

Table 5: Interpretation of FTIR peak of Irbesartan solid dispersion

Obtained peak	Interpretation	
	Functional group	Standard range
C=O	1625	1725-1705
Amine(2)	3458	3500-3100
CH_3	1496	1450-1375
ALKENE	3070	3100-3000

CONCLUSION

The poor aqueous solubility of Irbesartan is the challenge that has been tried to rectify in this study. The application of the mixed hydrotropic concept is investigated to solve the solubility issue associated with Irbesartan. The individual hydrotrope solution has shown a significant rise in aqueous solubility which is further influenced by the combination of hydrotropes. The enhancement in solubility of Irbesartan through the formation of Hydrotropic solid dispersion has resulted three hundred and eighty four times greater solubility than that of in water alone. The mixed hydrotropic blend with a 0:15:0:15 concentration ratio of sodium benzoate : sodium citrate was optimized based on results obtained from solubility study conducted by shake flask method. The selection and variation of various hydrotropes and their concentration remains wide open for further investigation in future.

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