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Research Article

SOLID DISPERSIONS – AN APPROACH TO ENHANCE THE DISSOLUTION RATE OF IRBESARTAN

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ABSTRACT

Irbesartan is a non peptide specific competitive antagonist of the angiotensin II receptor (AT1 subtype) used orally for treatment of hypertension. The first approved indication for irbesartan is hypertension. Irbesartan is a white to off-white crystalline powder with a molecular weight of 428.5. Irbesartan is slightly soluble in alcohol and methylene chloride and practically insoluble in water. The drug exhibits low bioavailability related to its poor water solubility. Irbesartan is a class II compound, i.e., water-insoluble, lipophilic, and highly permeable according to Biopharmaceutical Classification System. The purpose of this study was to prepare and characterize solid dispersions of the poorly water soluble anti hypertensive irbesartan with water soluble carrier such as dextrose to improving its dissolution properties. The solid dispersions were prepared by co-grinding and melt fusion method. Evaluation of the dispersions was performed using dissolution studies, the results obtained showed that the rate of dissolution of irbesartan was considerably improved when formulated in solid dispersions as compare to pure drug.

Keywords: Irbesartan, solid dispersions, dextrose and rate of dissolution**.**

INTRODUCTION

The bioavailability of poorly water-soluble drugs is often limited by its dissolution rate, which in turn is controlled by the surface area available for dissolution. The effect of the particle size of a drug on its dissolution rate and biological activity is well known. For example, the micronization of griseofulvin resulted in reduction of the therapeutic dose by half[1]. The conventional methods for reducing particle size or increasing surface area include trituration, grinding, micronization, and controlled precipitation[2]. Co - precipitates and melts are solid dispersions that provide a means of reducing particle size to the molecular level.

Sekiguchi and obi[2] first introduced the concept of using solid dispersions to improve bioavailability of poorly water-soluble drugs in 1961. They demonstrated that the eutectic mixture of sulphathiazole and the physiologically inert water-soluble carrier urea exhibited higher absorption and excretion after oral administration when compared with sulphathiazole alone. Recent work on solid dispersions has been extended for the

development of sustained release preparations also.

Definition

Chiou and Regelman[1] defined the term solid dispersion as a dispersion of active ingredients in an inert carrier or matrix at solid state prepared by the melting (fusion), solvent or melting-solvent method. Dispersions obtained through the fusion process are often called melts, and those obtained by the solvent method are frequently referred to as co precipitates or co - evaporates. Examples include sulfathiozole-povidone and reserpine – PVP solid dispersions[4].

Methods of preparation of solid dispersions

The two basic procedures used to prepare solid dispersions are the fusion and co - solvent techniques. Modifications of these methods and combination of them have also been use [2]. Recently, application of supercritical fluid has been explored to form pharmaceutical solid dispersions[5].

Classification

Chiou and Regelman[1] classified solid dispersions into the following six representative types **1)**Simple eutectic mixtures, 2)Solid solutions, 3)Glass solutions and glass suspensions, 4)Amorphous precipitations in a crystalline carrier, 5) Compound or complexes, 6)Combinations of the previous five types

Many techniques have been used to characterize the physical nature of solid dispersions. These include thermal analysis (e.g.; cooling-curve, thaw-melt, differential scanning calorimetry, x-ray diffraction, microscopic, spectroscopic, dissolution rate, and thermodynamic methods.) Usually, a combination of two or more methods is required to obtain a complete picture of the solid dispersion system.

Mechanism of increased dissolution rate

The enhancement in dissolution rate as a result of solid dispersion formation, relative to pure drug, varies from as high as 400 fold to less than two fold[6] Corrigan[7] reviewed the current understanding of the mechanisms of release from solid dispersions. The increase in dissolution rate for solid dispersions can be attributed to a number of factors. It is very difficult to show experimentally that any one particular factor is more important than another is. The main reason postulated for the observed improvements in dissolution of these systems are as follows.

1. Reduction of particle size

In the case of glass, solid solutions, and amorphous dispersions, particle size is reduced to a minimum level. This can result in an enhancement of dissolution rate due to increase in the surface area for solubilization.

2. Solubilization effect

The carrier material as it dissolves may have a solubilization effect on the drug. This was shown to be the case of paracetamol and chlorpropamide as well as for numerous other drugs[8].

3. Wettability and dispersability

The carrier material may also have an enhancing effect on the wettability and dispersability of the drug in the dissolution media. This retards any agglomeration or aggregation of the particles, which can slow the dissolution process.

4. Meta stable forms

Formation of metastable dispersions with reduced lattice energy would result in faster dissolution rates. It was found that the activation energies for dissolution for furosemide were 17 Kcal / mole, where as for 1:2 furosemide: pvp co precipitate, it was only 7.3 Kcal / mole[9].

Selection of the carrier

The properties of a carrier have a major influence on the dissolution characteristics of the dispersed drug. A carrier should meet the following criteria to be suitable for increasing the dissolution rate of drug.

1. Be freely water soluble with intrinsic rapid dissolution properties.
2. Be nontoxic and pharmacologically inert.
3. Be heat stable with a low melting point for the melt method.
4. Be soluble in a variety of solvents and pass through a vitreous state upon solvent evaporation for the solvent method.
5. Be able to preferably increase the aqueous solubility of the drug.

6. Be chemically compatible with the drug and not form a strongly bonded complex with the drug.

MATERIALS AND METHODS

Analytical Methods

A number of methods are reported in the literature for the estimation of irbesartan. These methods include spectrophotometric method[27-29] derivative spectrophotometry[30]. Spectrophotometric method (US FDA) was used in the present project work for the estimation of irbesartan at 244 nm in 0.1N HCl[34].

Materials

Irbesartan a gift sample of Hetero drugs, Hyderabad, Ethanol (qualigens), Hydrochloric Acid (qualigens), Distilled water.

Standard solution

50 mg of irbesartan was dissolved in ethanol in a 50 ml volumetric flask and the solution was made up to mark with ethanol.

Procedure

The standard solution of irbesartan was subsequently diluted with 0.1 N hydrochloric acid to obtain a series of solutions containing 2, 4, 8, 12, 16, and 20 µg of irbesartan per ml. The absorbance of the solutions was measured in ELICO-SL 150 UV Spectrophotometer at 244 nm using 0.1 N hydrochloric acid as a blank.

Phase Solubility Studies

Phase solubility studies on irbesartan were performed by the method of Higuchi and Connors [35]. 100 mg of irbesartan was added to a series of dextrose solutions (50 ml each) in 0.1N HCl. The dextrose concentration varied from zero to 600 mg / 100 ml. The conical flasks containing the above systems were shaken on a water bath shaker for 48 hours at 37 ^{0}C. The systems were allowed to stand for 24 hours, so that irbesartan in undissolved form is in equilibrium with the dissolved form. The systems were filtered using whatmanns paper, the filtrate was suitably diluted and analyzed spectrophotometrically at 244 nm. Phase solubility studies were carried in triplicate[36].

Preparation of Solid Dispersions

Materials

Irbesartan (Hetero drugs), Dextrose (chemi labs), Hydrochloric acid (qualigens), Distilled water.

Methods

The solid dispersions were prepared by co-grinding method and melt method. Irbesartan and dextrose were mixed in various ratios (1:1, 1:5, 1:10, 1:15 and 1:20) on molar ratios basis.

Method of preparation of dispersion by co-grinding method

The required quantities of drug and carrier as given in table. 2 Were triturated in a mortar thoroughly for 20 min. The obtained powder blend was sifted thorough sieve number 80. Solid dispersion equivalent to 50 mg irbesartan was filled into capsules.

Method of preparation of dispersion by melt and fusion method

The required quantities of irbesartan as given in table 2 were melted in a stainless steel crucible on a sand bath, and then carrier dextrose was added to the molten drug. After dextrose also melted the molten mass was thoroughly mixed with a glass rod and was immediately placed on an ice bath for solidification. The mass obtained was crushed, pulverized and sifted through mesh no 80. Solid dispersion equivalent to 50 mg of irbesartan was filled into capsules.

Formulations C to G were prepared by co-grinding method and Formulations H to L were prepared by melt method. The ratio in the bracket indicates the proportion of irbesartan and dextrose on molar basis in the formulation.

Evaluation of solid dispersions

The solid dispersions prepared were evaluated by determined the Drug content, Dissolution rate.

Assay of Drug Content

Solid dispersion equivalent to 50 mg of irbesartan was weighed into a 50 ml volumetric flask; 25 ml ethanol was added and the contents were sonicated for 10 minutes to dissolve the solid dispersion. This solution was suitably diluted with 0.1 N HCl and was assayed at 244 nm for irbesartan.

Dissolution Rate Studies

The dissolution rate testing of different irbesartan capsule formulations (table 3) was studied using USP XX1 dissolution rate testing apparatus, (basket type) (LAB INDIA DISSO 2000). The basket was rotated at a speed of 50 rpm and the dissolution fluid (1000 ml 0.1N HCl) was maintained at a temperature of $37.5^0 \pm 0.5\ ^0C$. At specific time intervals, a 5 ml aliquot of dissolved medium was withdrawn and was replaced with fresh quantity of dissolution medium. The samples were suitably diluted with dissolution medium and assayed for irbesartan content by measuring the absorbance at 244 nm using U.V Spectrophotometer (ELICO SL 159).

RESULTS AND DISCUSSION

Analytical Methods

The absorbances of the various solutions are given in table 4. The absorbances were plotted against concentrations of irbesartan (graph 1). This calibration curve was used to determine the amount of irbesartan in unknown solutions.

Phase Solubility Studies

The results of the phase solubility studies are given in table 5 and graph 2.

From graph 2 it can be concluded that the solubility of irbesartan increased linearly with concentration of dextrose. This could be due to hydrotrophy. Hydrotrophy refers to the ability of a chemical compound to increase the aqueous solubility of another compound (usually a sparingly soluble organic compound). Compounds that have this property are called "hydrotropes".

Assay of drug content

All the solid dispersions prepared by co-grinding and melt method were found to contain 95 % to 105 % of the amount that they should contain. The assay results of various formulations are given in the table 6.

Dissolution

The consolidated dissolution profiles of irbesartan from various formulations are given in the tables 7 to 9 and graphs 3 to 5.

CONCLUSION

Solid dispersions of irbesartan (L) prepared using dextrose by melt method was found to perform better than the pure drug and the branded formulations XARB-150, IROVEL-150 with respect to dissolution. It is very likely that the in vivo bioavailability of formulation **L** will be better than the branded forms of irbesartan. However an in-vivo study is needed to prove that.

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Table 1: Materials Used as Carriers for Solid Dispersions[15]

S. No.	Class	Examples
1	Sugars	Dextrose, sucrose, galactose, sorbitol, maltose, xylitol, mannitol, and lactose.
2	Acids	Citric acid, succinic acid.
3	Polymeric materials	Povidone (PVP), polyethylene glycols (PEG), hydroxy propyl cellulose.
4	Insoluble or enteric Polymers	Hydroxy propyl methylcellulose phthalate (HPMCP), eudragit L-100, eudragit S-100, Eudragit RL, and RS.
5	Surfactants	Polyoxy ethylene sterate, Renex, Poloxamer188, TexaforAIP, Tweens and Spans.

Table 2: Amount of Irbesartan and Dextrose in Solid Dispersions

S. No.	Formulation	Amount of Irbesartan (mg)	Amount of dextrose (mg)
1	C (1:1)	214	99
2	D (1:5)	214	495
3	E (1:10)	214	990
4	F (1:15)	214	1485
5	G (1:20)	214	1980
6	H (1:1)	214	99
7	I (1:5)	214	495
8	J (1:10)	214	990
9	K (1:15)	214	1485
10	L (1:20)	214	1980

Table 3: List of Different Irbesartan Capsule Formulations

S. No.	Formulation	Composition/ brand
1	A	IRB (pure)
2	B	IRB(melt)
3	C	IRB:DEXTROSE (1:1)
4	D	IRB:DEXTROSE(1:5)
5	E	IRB:DEXTROSE(1:10)
6	F	IRB:DEXTROSE(1:15)
7	G	IRB:DEXTROSE(1:20)
8	H	IRB:DEXTROSE (1:1)
9	I	IRB:DEXTROSE(1:5)
10	J	IRB:DEXTROSEI(1:10)
11	K	IRB:DEXTROSE(1:15)
12	L	IRB:DEXTROSE(1:20)
13	M	IRB(XARB-150)
14	N	IRB(IROVEL-150)

Table 4: Absorbance of Irbesartan Standard Solutions

S. No.	Concentration µg /ml	Absorbance at 244nm				RSD
		Trial I	Trial II	Trial III	Average & s.d.	
1	0	0.000	0.000	0.000	0	0
2	2	0.107	0.119	0.125	0.1 ± 0.009	0.09
3	4	0.205	0.202	0.212	0.2 ± 0.005	0.03
4	8	0.391	0.403	0.410	0.4 ± 0.010	0.03
5	12	0.594	0.602	0.612	0.6 ± 0.009	0.02
6	16	0.801	0.813	0.808	0.8 ± 0.006	0.01
7	20	0.989	0.995	0.991	0.9 ± 0.003	0.01

Table 5: Phase Solubility Studies of Irbesartan

Concentration of dextrose in 0.1 N HCl. (mg / 100ml)	Solubility of irbesartan in dextrose solution, mg / 100 ml.				s.d.	% RSD
	Trial 1	Trial 2	Trial3	Average		
0	73.18	72.42	74.94	73.51	1.2	0.01
200	82.50	78.50	77.12	79.37	2.7	0.03
400	83.08	82.04	84.6	83.24	1.2	0.01
600	88.46	87.04	88.02	87.84	0.7	0.01

Table 6: Assay of Irbesartan Content in Solid Dispersion Formulations

Formulation	Concentration (mcg / ml)	mg of irbesartan in powder mixture	% Assay
B	9.56	47.80	95.61
C	9.89	49.49	98.99
D	9.92	49.6	99.2
E	9.92	49.63	99.2
F	9.91	49.56	99.1
G	9.93	49.66	99.3
H	9.85	49.26	98.5
I	9.99	49.99	99.9
J	9.79	48.96	97.9
K	9.97	49.85	99.7
L	9.94	4.73	99.46

Table 7: Dissolution Profiles of Irbesartan from Capsules Containing Pure Irbesartan and Co- Grinding Formulations

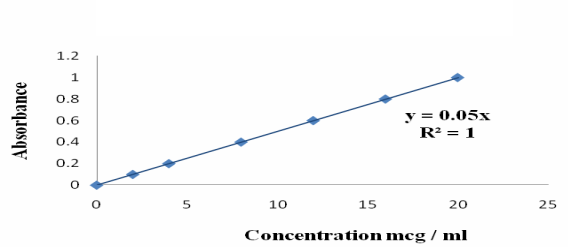
S.No	Time (Min)	% Irbesartan Dissolved						
		A	B	C	D	E	F	G
1	0	0	0	0	0	0	0	0
2	10	13.58	7.76	9.98	16.06	70.25	71.75	83.16
3	20	15.9	11.35	17.18	23.41	78.17	81.6	86.45
4	30	19.49	14.93	26.38	35.04	84.01	91.78	91.31
5	45	21.88	18.28	38.06	52.67	92.84	95.19	97.49
6	60	26.65	24.07	46.08	65.16	97.4	97.59	99.58

Table 8: Dissolution Profiles of Irbesartan from Capsules Containing Pure Irbesartan and Melt Formulations

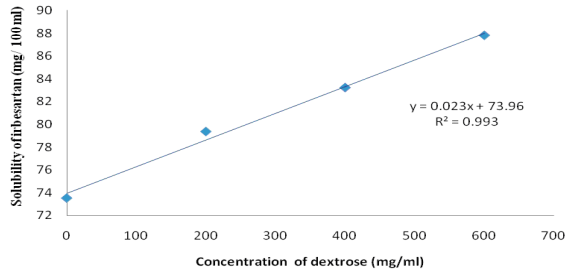
S.No	Time mins	% Irbesartan dissolved						
		A	B	H	I	J	K	L
1	0	0	0	0	0	0	0	0
2	10	13.58	7.76	14.35	20.35	22.76	77.52	87.09
3	20	15.9	11.35	25.12	29.84	59.45	83.09	92.77
4	30	19.49	14.93	35.37	39.23	92.07	93.34	96.36
5	45	21.88	18.28	47.34	61.75	98.2	97.94	98.89
6	60	26.65	24.07	63.21	81.58	99.57	99.47	99.8

Table 9: Dissolution Profiles of Irbesartan from Capsules Containing PureIrbesartan(A) Best Formulations Prepared(G,L), Marketed formulations (M,N)

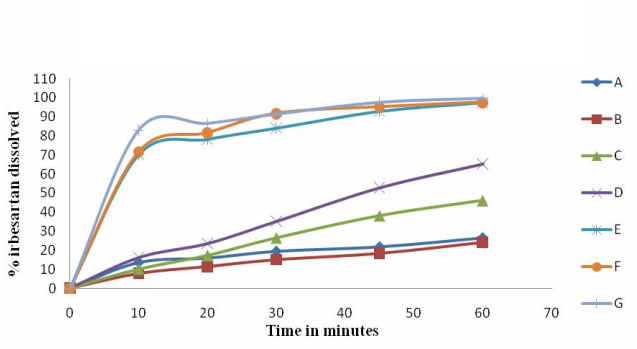
S. No.	Time mins	% Irbesartan Dissolved				
		A	G	L	M	N
1	0	0	0	0	0	0
2	10	13.58	83.16	87.09	64.53	68.15
3	20	15.9	86.45	92.77	84.4	85.25
4	30	19.49	91.31	96.36	93.27	94.13
5	45	21.88	97.49	98.89	97.47	95.95
6	60	26.65	99.58	99.8	99.02	98.84



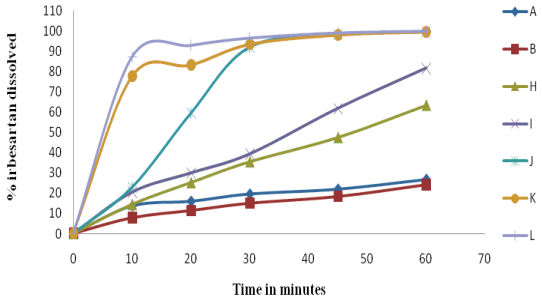
Graph 1: Calibration Curve of Irbesartan in 0.1N HCL at 244nm



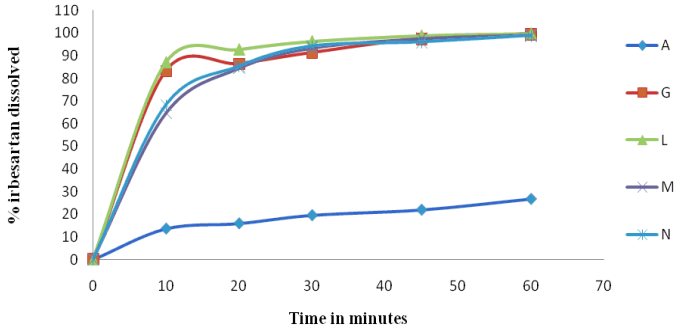
Graph 2 : Phase Solubility of Irbesartan-Dextrose in 0.1N HCl



Graph 3: Dissolution profiles of Irbesartan from Capsules containing pure Irbesartan and co-Grinding Formulations



Graph 4: Dissolution Profiles of Irbesartan from Capsules Pure Irbesartan and Melt Formulations



Graph 5: Dissolution profile of irbesartan from Capsules Containing Pure Irbesartan (A) best Formulations Prepared (G,L), Marketed Formulations (M,N)

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