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EVALUATION OF ANTIHYPERTENSIVE ACTIVITY OF IRBESARTAN SOLID DISPERSIONS BY NON-INVASIVE TECHNIQUE

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ABSTRACT

Aim: *Solid dispersions in hydrophilic carriers have attracted considerable interest of improving the dissolution rate and possibly bioavailability of a range of hydrophobic drugs. The aim of present study was made to improve the solubility of Irbesartan by formulating into solid dispersions by using a polymer, kollidon VA64, was further subjected to anti- hypertensive evaluation in Wistar rats.* ***Method:*** *Solid dispersions were prepared by using physical mixing, solvent evaporation and kneading methods using Kollidon VA64 as a polymer at different ratios. All the solid dispersions were found to be stable and evaluated for drug release studies.* ***Results:*** *Majority of the formulations displayed first order release kinetics and were found to be linear with R^2 values in the range of 0.991-0.994. FTIR and DSC analysis results revealed no major interactions between the drug and the excipients used in the solid dispersions. The optimized solid dispersion was evaluated for its antihypertensive activity by using noninvasive tail cuff method.* ***Conclusion:*** *It was observed that Irbesartan solid dispersion (IK3) showed more anti-hypertensive activity in deoxycorticosterone acetate (DOCA) salt induced hypertensive rats than glucose induced hypertensive rats when compared with standard Irbesartan and other formulations.*

KEY WORDS

Irbesartan, solid dispersions, Kollidon VA64, Kneading method.

INTRODUCTION:

In Pharmaceutical companies' major work is going in the field of drug discovery, in the anticipation of finding new therapeutic approaches and improving drugs for existing therapeutic areas. Among the five key physicochemical properties in the early compound screening including pKa, solubility, permeability, stability and lipophilicity, poor solubility tops the list of undesirable compound properties [1]. It is a well-established fact for poorly water-soluble drugs that the rate-limiting step in their absorption process is dissolution rate in the gastrointestinal fluids rather than the rapidity of their diffusion across the gut wall by improving the release profiles of such drugs, it is possible to enhance their bioavailability and reduce side effects.[2] Compounds exhibiting dissolution rate limited bioavailability are considered class II according to BCS classification [3]. As per recent reports, 49 % of the total NDAs filled in between 1995 to 2010 was BCS class IV, while only 8 % were BCS class II drugs, revealing that a majority of approved new drugs were water insoluble. There are drugs that have poor solubility in water but can be dissolved by suitable conventional formulation strategies which include, co-solvents, milling techniques, super critical processing. Solid dispersions including complexation and precipitation techniques. Solid dispersion technique has often proved to be the most commonly used in improving dissolution and bioavailability of poorly soluble active pharmaceutical ingredients because it is simple, economic and advantageous. In solid dispersion technique, water soluble carriers are used to improve dissolution characteristics of poorly water-soluble drugs [4]. Solid dispersions are dispersion of the active pharmaceutical

ingredient in an inert carrier or a matrix in the solid state. Concept of solid dispersion was introduced first by Sekiguchi and Obi in 1961 [5& 6]. The solubility of the drug increased with increase in the concentration of the carrier [7].

Hypertension (HTN or HT), also known as high blood pressure (HBP), is a long-term Medical condition in which the blood pressure in the arteries is persistently elevated [8]. High blood pressure usually does not cause symptoms [9]. Long term high blood pressure; however, is a major risk factor for coronary artery disease, stroke, heart failure, peripheral vascular disease, vision loss, and chronic kidney disease [10&11]. Blood pressure is expressed by two measurements, the systolic and diastolic pressures, which are the maximum and minimum pressures, respectively [12]. Normal blood pressure at rest is within the range of 100–140 millimeters mercury (mmHg) systolic and 60–90 mmHg diastolic [13]. High blood pressure is present if the resting blood pressure is persistently at or above 140/90 mmHg for most adults [14]. Antihypertensive are a class of drugs that are used to treat hypertension (high blood pressure) [15]. Antihypertensive therapy seeks to prevent the complications of high blood pressure, such as stroke and myocardial infarction. Evidence suggests that reduction of the blood pressure by 5 mmHg can decrease the risk of stroke by 34% ischemic heart disease by 21%, and reduce the likelihood of dementia, heart failure, and mortality from cardiovascular disease [16].

Angiotensin II receptor antagonists, selectively block the Angiotensin, thus reducing the number of Angiotensin II receptors available to bind to AIL8. Pharmacologic differences exist between drugs within this class that could result in different clinical profiles. This is especially true for duration of action. A sustained and smooth blood pressure-lowering effect is important to provide optimal protection against cardiovascular complications.

Irbesartan, an angiotensin II receptor antagonist indicated for the treatment of hypertension, has been found to be well tolerated and effective in reducing blood pressure in a dose-dependent manner [17]. Irbesartan appears to be eliminated in a biphasic manner with a terminal elimination half-life ($t_{1/2}$) of approximately 11-15 h. Irbesartan shows linear pharmacokinetics over the therapeutic dose range. Steady state levels of Irbesartan are achieved within 3 days and limited accumulation (20%) was observed in plasma upon repeated once daily dosing. The absolute bioavailability of Irbesartan is approximately 60-80%. Following oral administration, the peak plasma concentration (C_{max}) of Irbesartan is reached after 1.5-2h [18]. The drug selected for the present investigation was Irbesartan, which is a BCS class- II drug with poor aqueous solubility. Hence it is necessary to enhance its solubility. In the present study, an attempt was made to improve the solubility of Irbesartan by formulating as solid dispersions by using Kollidon VA64. The optimized solid dispersion was further subjected to anti-hypertensive evaluation in Wister rats.

MATERIALS AND METHODS:

Irbesartan was obtained as a gift sample from Mylan Laboratories Limited, Hyderabad. Kollidon VA64 as a gift sample from M/s. NATCO pharma Ltd, Hyderabad. All other chemicals and reagents were of analytical grade.

Saturated solubility studies:

Saturated solubility studies of Irbesartan were performed in different dissolution media. 500 mg of Irbesartan was weighed and transferred into separate conical flasks. 50 ml of different dissolution media were transferred into individual conical flask and were closed appropriately. All conical flasks were placed in the orbital shaker with an rpm of 50 and temperature at 37°C ± 1°C for 24h [19]. Then the conical flasks were removed from the orbital shaker and the samples were filtered by using Whatmann filter paper. The clear solution obtained by filtration was suitably diluted with appropriate dissolution media and the absorbance values were noted at 244 nm by using corresponding dissolution media as blank solutions.

Preparation of solid dispersions:

Irbesartan solid dispersions with Kollidon VA64 were prepared by using three methods such as:

Physical mixing:

Specified quantity of Irbesartan and Kollidon VA64 were weighed separately and passed through sieve no. 80. The materials passed through sieve no. 80 were collected and transferred into a clean and dry glass mortar. Irbesartan and kollidon were triturated together for 5 min and again screened through sieve no. 80. The mixture passed through sieve no. 80 was collected, packed in a wide mouthed amber colored glass container and hermetically sealed [20].

Solvent evaporation:

Specified quantity of Irbesartan and Kollidon VA64 were taken in a china dish and 3ml of methanol was added and slightly heated until both drug and polymer dissolved. Then it is subsequently allowed to evaporate. The obtained mixture was dried, passed through the sieve no. 80, packed in a wide mouthed amber colored glass container, hermetically sealed and stored [21].

Kneading method:

In this method, Irbesartan and Kollidon VA64 were taken in a glass motor and 3ml of water was added and triturated vigorously until damp mass was obtained. Then the mass was dried at room temperature, the mixture was passed through sieve no. 80, packed in a wide mouthed amber colored glass container and hermetically sealed [22]. The composition of various solid dispersions was given in table 1.

Table 1: Compositions of Various Solid Dispersions of Irbesartan

Composition		Ratio (Irbesartan: Kollidon VA64)
Physical method	IPH-1	1:1
	IPH-2	1:2
	IPH-3	1:3
Solvent evaporation method	IS-1	1:1
	IS-2	1:2
	IS-3	1:3
Kneading method	IK -1	1:1
	IK -2	1:2
	IK -3	1:3

***One part is equal to 150mg**

Evaluation of solid dispersions:

Solid dispersions prepared by using various methods were evaluated for particle size, flow properties and the drug content. Particle size was determined by sieve analysis and flow properties of solid dispersions were determined by angle of repose and Carr's index.

Estimation of Irbesartan in solid dispersions:

Solid dispersions of Irbesartan from a batch were taken at random and were transferred into a 100 ml volumetric flask, 70 ml of methanol was added and shaken occasionally for about 30 min. Finally, the volume was made up to 100 ml by adding methanol. About 10 ml of the solution from the volumetric flask was taken and centrifuged. The supernatant solution from the centrifuge tube was collected and filtered by using whatmann filter. Then the filtrate was subsequently diluted with 1.2 pH buffer and the absorbance was measured at 244 nm.

Dissolution rate studies on Irbesartan:

Dissolution studies in each solid dispersion were performed in a calibrated 8 station dissolution test apparatus (LABINDIA DS 8000) equipped with paddles (USP apparatus II) employing 900 ml of 1.2 pH as a dissolution media. The samples were withdrawn at 5, 10, 15, 20, 30, 45- & 60-min. Fresh volume of the medium was replaced with the withdrawn volume to maintain the sink conditions and constant volume throughout the experiment. Samples withdrawn were suitably diluted with same dissolution medium and the amount of drug dissolved was estimated by double beam spectrophotometer. The dissolution studies on each formulation were conducted in triplicate. Based upon the data obtained from the dissolution studies various parameters such as T_{50}, T_{90}, zero order and first order release rate constants were estimated. The *in - vitro* dissolution parameters were given in Table 2.

Table 2: Dissolution parameters of Irbesartan optimized solid dispersions

S. No	Solid Dispersion	% Drug Released at 60mins	T_{50} (min)	T_{90} (min)	DE 30%	First Order R^2
1	IPD	41.43	>60	>60	53.8	0.9142
2	IP3	53.4	43	>60	35	0.9442
3	IS3	60.15	21.5	>60	43.3	0.9761
4	IK3	64.62	11	>60	48.3	0.9962

The dissolution profiles of solid dispersions were shown as Figure 1.

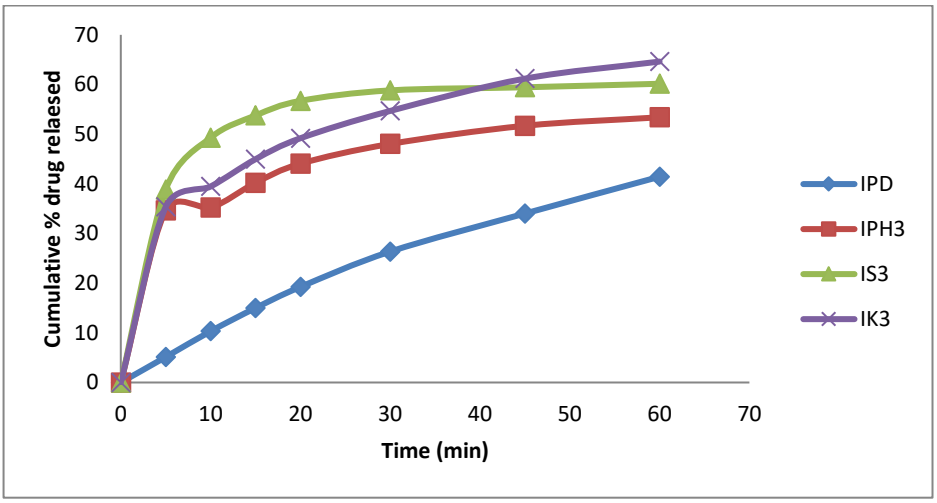

Figure 1: Comparative dissolution profile of Irbesartan solid dispersions

ANTI- HYPERTENSIVE ACTIVITY:

Experimental animals:

Male Wister rats (n=6) of weighing 150-200gms were used for the present study. The rats were housed in polypropylene cages under 12hrs light / dark cycle, fed with standard laboratory chow (Hindustan lever limited, Mumbai) and water *ad libitum*. Animals were acclimatized to the laboratory conditions prior to experimentation.

All the experimental procedures and protocols used in study were reviewed and approved by the Institutional Animal Ethical Committee (IAEC) of Chebrolu Hanumaiah Institute of Pharmaceutical Sciences and care of laboratory animals was taken as per the guidelines of Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA). (Approval no.1529/Po/Re/11/CPCSEA/CHIPS/IAEC/PRO-03/2015-16).

Anti-Hypertensive Study Using Glucose and DOCA Salt Induced Hypertensive design (Drugs and Groups):

Drugs: Irbesartan solid dispersion, Irbesartan pure drug.

Determination of antihypertensive activity by Glucose-induced hypertensive rat model:

Male Wistar rats were randomly assigned into four groups (n = 6). Group 1 received normal vehicle only. Group 2 received 10 % glucose solution instead of water for 21 consecutive days. Group 3 received 10 % glucose solution and an aqueous Irbesartan solid dispersion (0.52 mg/kg) for 21 consecutive days. Group 4 received 10 % glucose solution and an aqueous Irbesartan standard drug Animals were fed on standard diet. Blood pressure and heart rate of these groups were measured on week 0, 1, 2, and 3.

Determination of antihypertensive activity by DOCA-Salt model of hypertension:

The animals were divided into four groups (n = 6). Group 1 received normal vehicle only. Group 2 received 10 mg DOCA/rat subcutaneously by alternate days for 6 weeks and 1% NaCl. Group 3 received 10 mg DOCA/rat subcutaneously by alternate days for 6 weeks, 1% NaCl and an aqueous Irbesartan solid dispersion (0.13 mg/kg). Group 4 received 10 mg DOCA/rat subcutaneously by alternate days for 6 weeks, 1% NaCl and an aqueous Irbesartan standard (pure) drug. DOCA was dissolved in sesame oil. Blood pressure and heart rate of these groups were measured on week 0, 1, 2, and 6.

Measurement of systolic blood pressure by noninvasive technique:

Sphygmomanometer, with coupler, pulse transducer, tri-way and non-collapsible rubber tubes were procured and inflatable raft tail-cuff was designed in CHIPS Laboratory Figure 2.

Figure 2: Measurement of Systolic Blood

Pressure by Noninvasive Technique

The cuff consists of latex balloon measuring 5 × 2 cm with 0.5 mm thickness. This balloon was placed in a circular plastic case having a diameter of 23 mm with a central hole of 12 mm diameter. The balloon was kept in such a fashion that it remains in contact with an inner surface of plastic case around the central hole, so that this balloon encircles the tail. One end of the tri way was connected with the balloon (tail- cuff) and other two ends were connected to inflating-deflating pump and sphygmomanometer measures systolic BP by determining the cuff pressure (reflected on sphygmomanometer) at which blood flow (pulse) to the tail was eliminated. The animals were kept in restrainers after acclimatizing them, the tail was passed through the hole of the newly designed cuff and the pulse transducer was tied around the tail distal to the cuff, the cuff was inflated by the pump and the pressure in the cuff was raised until the pulse was eliminated. The pressure at which the pulse was eliminated was the systolic BP of the animal.

Statistical analysis:

The results were expressed as mean ± standard error of mean (SEM) and statistical analysis was carried out by two way analysis of variance (ANOVA) followed by Dunnet's multiple comparision test using Graph Pad Prism. Differences were considered Significant at ($p < 0.05$).

Characterization:

Based on the dissolution studies performed on all the formulations, the optimized formulations were selected for further investigation such as Fourier Transform Infrared (FTIR) spectroscopy and differential scanning colourimetry (DSC). The FTIR & DSC thermogram of Solid dispersions were shown in Figures 3 & 4.

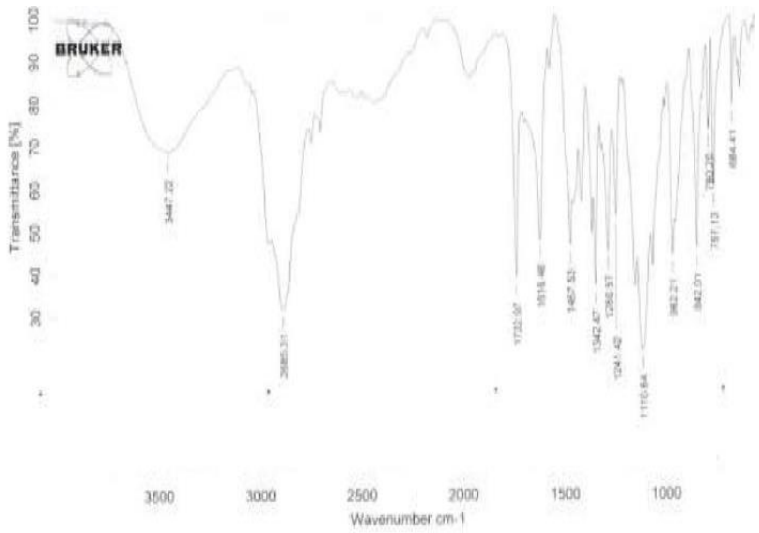

Fig3: FTIR of a) Irbesartan

Fig3: FTIR of b) Ik3

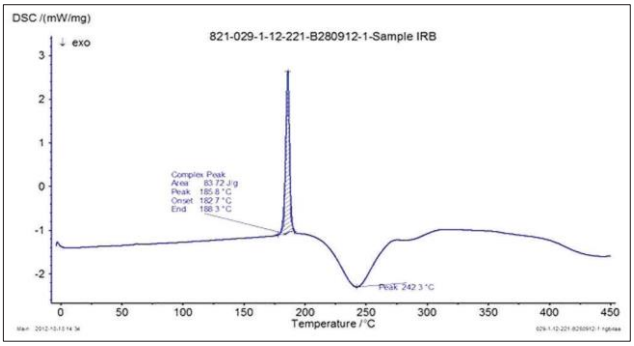

Figure 4: Differential scanning Calorimetry thermo gram of (a) Irbesartan pure drug (b) Ik3

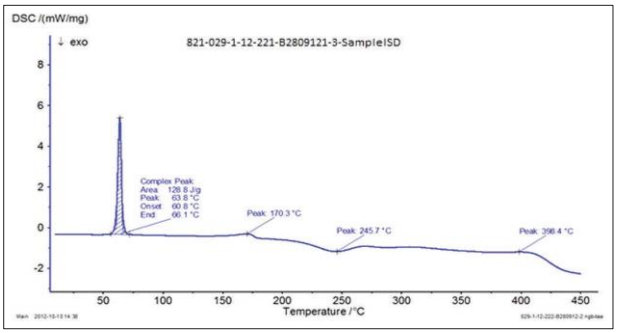

Figure 4: Differential scanning Calorimetry thermo gram of (b) Ik3

RESULTS AND DISCUSSION:

Saturated solubility studies revealed that Irbesartan show maximum solubility in 1.2 pH buffer medium than the dissolution medium used. Hence, it was selected as dissolution medium for further studies. The solid dispersions were prepared by physical mixing, kneading and solvent evaporation methods by using Kollidon VA64 as carrier. All dispersions were prepared under similar conditions to avoid batch to batch variation. The compositions of solid dispersions are shown in Table 1.

The dispersions were found to be uniform in their characteristics. The angle of repose and the Carr's index values of all the solid dispersions were in the range of 27.04°- 38.02° and 15-35% respectively. The drug content in all solid dispersions was highly uniform in the range of 97.10 ± 0.9 - 99.95 ± 0.3% indicated the uniformity. The Dissolution studies of Irbesartan solid dispersions prepared were performed using 1.2 pH buffer by paddle method. The dissolution study of solid dispersions were found to be rapid than Irbesartan pure drug. The T_{50}, T_{90} and $DE_{30\%}$ values of all the formulation

indicated there rapid drug dissolution than the pure drug of irbesartan. The drug release profiles of the prepared solid dispersions were shown in the Figure 1.

It was also observed that concentration of Kollidon VA64 increase the rate of dissolution of drug was also increased. Solid dispersions prepared by kneading method using drug to carrier ratio of 1:3 was found to undergo rapid dissolution rates than the others. Among IPH, IS solid dispersions, IK3 released the drug rapidly than the pure drug and other solid dispersions. Increase the drug release of solid dispersions prepared by various methods were in the order of Kneading> solvent evaporation> Physical mixing methods. The kinetics of drug release from all the formulation follows first order kinetics and the results were shown in Table 2.

Hence, solid dispersion IK3 was characterized by FTIR, DSC and *in-vivo* studies were conducted. The characteristic absorption peaks of IBS was found at 3055 cm^{-1} and 3032 cm^{-1} (N–H stretch), 1731 cm^{-1} (C = O stretch), 1622 cm^{-1} (C–N stretch). The FT-IR study indicated that the characteristic peaks of Irbesartan which were also present in the Irbesartan solid dispersion. It showed that there is no interaction between drug and excipients which were further confirmed by DSC analysis. The DSC revealed that a broad endothermic peak was observed at 188.3°C.DSC thermogram of Irbesartan solid dispersion prepared by kneading method indicates that the drug is entrapped in the polymer. The FTIR & DSC thermogram of Solid dispersions were shown in Figures 3 & 4.

Evaluation of Anti-Hypertensive Activity:

Present study revealed the significant antihypertensive activity of Irbesartan solid dispersion in glucose and DOCA salt induced hypertensive rats. Glucose and DOCA salt causes elevation of blood pressure by activation of the renin-angiotensin system. Renin acts on angiotensinogen (renin substrate), an α2- globulin to release the decapeptide angiotensin I. This decapeptide is cleaved by angiotensin converting enzyme (ACE) to yield the active angiotensin II (octapeptide) which is a potent vasoconstrictor leading to hypertension. Angiotensin II undergoes hydrolysis by an amino peptidase to yield the heptapeptide angiotensin III which is also active. Further cleavage yields to peptides with little activity. The protease rennin catalyzes the first and rate-limiting step in the formation of angiotensin II leading to acute hypertension. The results showed that, oral administration of Irbesartan solid dispersions significantly decreased the elevated blood pressure. In glucose induced Hypertensive rats, after 3 weeks of treatment, in DOCA salt induced Hypertensive rats, Irbesartan solid dispersion produced a significant anti- hypertensive effect after 6 weeks of treatment. Irbesartan solid dispersions when given to glucose induced and DOCA salt induced hypertensive rats more anti-hypertensive activity was observed when compared to Irbesartan pure drug due to increased solubility and increased amount of drug released. Pharmacological results of Irbesartan solid dispersions were shown in figures 2, 5 and 6 and values were given in the tables 3 and 4.

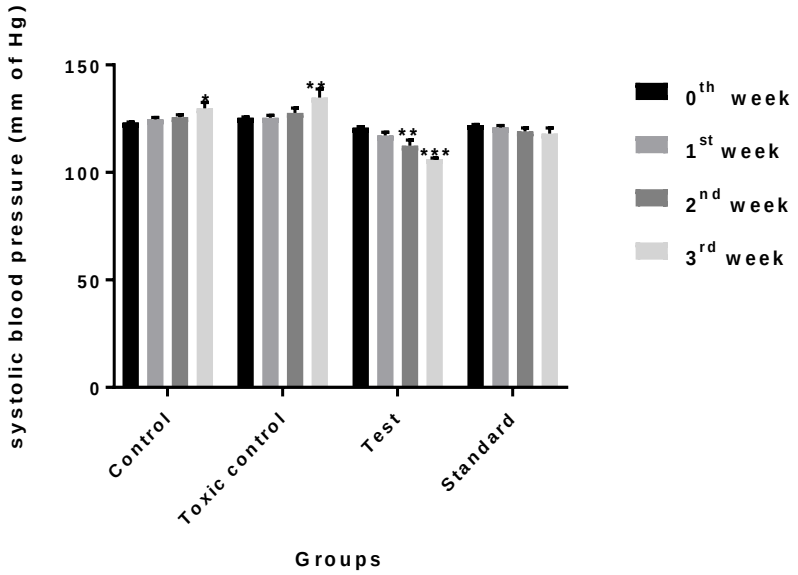

Figure 5: Hypotensive effect of Irbesartan

solid dispersion in glucose induced Hypertension

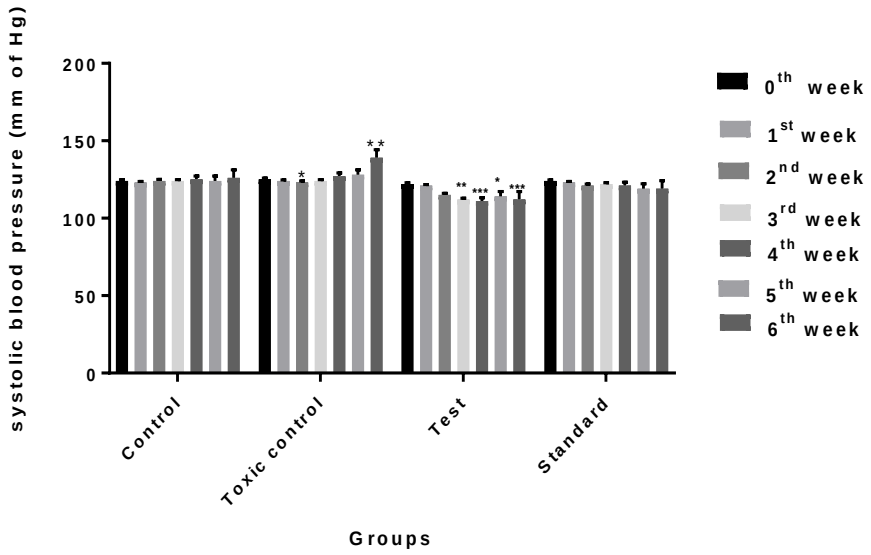

Figure 6: Hypotensive effect of Irbesatran

solid dispersion in DOCA salt induced hypertension

Table 3: Hypotensive activity of Irbesartan Solid dispersion in glucose induced Hypertensive rats

Groups	Hypertension (mm of Hg)			
	0th week	1st week	2nd week	3rd week
control	123.2±0.28	124.7±0.87	125.7±1.1	129.8±2.74
Toxic control (10% glucose solution)	125.4±0.47	125.4±1.11	127.7±2.2	134.8±4.04
10% glucose solution + Irbesartan solid dispersions(0.13mg/kg)	120.8±0.50	117.2±1.50	112.4±2.6	106.2±0.47
10% glucose solution+ Irbesartan pure drug	122±0.28	120.9±0.87	119.1±1.5	118±2.74

Data was analyzed by two-way ANOVA followed Dunnett's multiple test (P<0.05) compared to control

Table 4: Hypotensive activity of Irbesartan Solid dispersion in DOCA salt induced Hypertensive rats

Groups	Hypertension (mm of Hg)						
	0th week	1st week	2nd week	3rd week	4th week	5th week	6th week
Normal vehicle	124±0.99	123±0.672	121±1.09	122±0.97	122±2.26	121±3.26	122±5.21
Toxic control (DOCA salt)	125±0.99	124±0.672	123±1.09	124±0.97	127±2.26	128±3.26	139±5.21
DOCAsalt+ Irbesartan solid dispersion (0.13mg/ kg)	122±0.87	121±0.672	119±1.09	120±0.97	119±2.26	116±3.26	114±5.21
DOCA salt + Irbesartan pure drug	124±0.8	123±0.672	121±1.09	122±0.97	121±2.26	119±3.26	119±5.21

Data was analyzed by two-way ANOVA followed Dunnett's multiple test (P<0.05) compared to control

CONCLUSION:

The present study has shown that it is possible to increase the dissolution rate of poorly soluble drug Irbesartan by preparing it as solid dispersions with carrier like Kollidon VA64. Dispersions prepared by kneading method in the ratio of 1:3 for drug and carrier, exhibited rapid dissolution rate when compared with Irbesartan pure drug. Based on the dissolution studies performed on all the formulations, the optimized formulations were selected for further investigation such as FTIR, DSC analysis and *in-vivo* studies in Wistar rats. It revealed the significant antihypertensive activity of Irbesartan solid dispersion in glucose and DOCA salt induced hypertensive rats. Based on the above results, it may be concluded that the optimized Irbesartan solid dispersion showed more antihypertensive activity in DOCA salt induced hypertensive rats when compared with Irbesartan pure drug as a standard drug.

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