Research Article

FORMULATION AND EVALUTION OF IRBESARTAN LIQUISOLID TABLETS

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ABSTRACT

The main objective of this study is to improve the dissolution and there by availability of Irbesartan a practically insoluble drug by liquisolid Compact technique. The liquisolid tablets of Irbesartan were prepared by using various ratio of carrier (Avicel PH 102) to coating (Cab-O-Sil M5) material using PEG 400 as non volatile solvent. The prepared liquisolid tablets were evaluated for hardness, friability, disintegration time. The dissolution profile of Irbesartan tablets were determines according to USP method and compared to that of a direct compressible tablet. The formulated liquisolid system of Irbesartan exhibited acceptable flowability and compressibility. All the formula of liquisolid tablets showed more than 90% release within 60 minutes. Technique of Liquisolid tablet of Irbesartan which can be scaled-up industrially is promising approach for enhancing solubility and dissolution rate. This was due to an increase in wetting properties and surface of drug available for dissolution.

Keywords: Irbesartan, Liquisolid compact, dissolution rate.

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 water[1]. In addition, up to 50% of orally administered drug compounds suffer from formulation problems related to their low solubility and high lipophilicity[2-5].

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 AT_1 receptors is indicated for treatment of hypertension[6]. 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 molecule[7]. Solubility of IBS was found to be increased after complexation with polymer like β-CD[8].

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 solutions[9-10]. Amongst these the most promising method for promoting dissolution is the use of the liquisolid (LS) system[11-12]. Liquisolid systems are acceptably flowing and compressible powdered forms of liquid medications. The term 'liquid medication' involves oily liquid drugs and solutions or suspensions of water insoluble solid drugs carried in suitable nonvolatile solvent systems termed liquid vehicles. Employing this liquisolid technique, a liquid medication may be converted into a dry-looking, non-adherent, free flowing and readily compressible powder by a simple blending with selected powder excipients referred to as carrier and coating materials. Various grades of cellulose, starch and lactose may be used as the carriers, whereas very fine particle size silica powders may be used as the coating (or covering) materials[11]. In fundamental studies made by Spireas *et al.*, flow and compression issues have been addressed with the use of the new formulation mathematical model of liquisolid systems, which is based on the flowable (Φ-value) and compressible (Ψ -number) liquid retention potentials of the constituent powders. The good flow and compression properties of the liquisolid system are encouraged by the large surface area and fine particle size. Hence, liquisolid compacts containing water-insoluble drugs are expected to display enhanced dissolution characteristics and, consequently, improved oral bioavailability[13].

The aim of present work is to increase the solubility and in- vitro dissolution of practically insoluble drug IBS, by formulating in to liquisolid tablet consist of Avicel PH102, Cab-O–Sil and PEG 400 as liquid vehicle. The in-vitro release of such preparations were assessed and compared to that of conventional tablet using a USP dissolution apparatus II (paddle) in 900 ml 0.1N HCl pH 1.2 for 60 minutes.

MATERIALS AND METHODS

Materials

The following gift samples were received: IBS (Zydus Cadila Healthcare Limited., Mumbai); Avicel PH 102 (Reliance cellulose Pvt. Ltd. Hyderabad) and Cab-O-Sil (Cabot Corporation, North America, USA). The following samples were purchased propylene glycol (PG), polyethylene glycol 400 (PEG400), sodium starch glycolate (SSG) methanol. All reagents used were of analytical grade.

Methods

Saturation solubility studies

Solubility studies of IBS were carried out in distilled water, and PEG400. Saturated solutions were prepared by adding excess drug to vehicles, in Teflon facing screw capped vials. The vials were kept at equilibrium for period of 24 hrs on orbital shaking incubator (CIS-24, Remi instrument, Mumbai) at 37±0.5^{0}C and 100 rpm. The content of vials were filtered through 0.2 µm membrane filter and analyzed using UV spectrophotometer (1700, Shimadzu, Japan) at 244 nm. The results were extrapolated to determine the percent w/w of IBS in its saturated solution with the solvent under investigation.

Preparation of conventional tablet and liquisolid compacts

A conventional formulation of IBS (denoted as DC) was directly compressed into cylindrical tablets, each containing 40 mg drug. In addition, each DC tablet contained the following powder excipients: 170 mg Avicel PH 102, 70 mg lactose monohydrate, 30 mg Cab-O-Sil M5, and 40 mg SSG. A 10 tablet batch was mixed in a mortar for 10 min. and the final admixture was compressed using a manual compression machine.

Various liquisolid compacts containing 40 mg IBS were prepared by dispersing in nonvolatile vehicles PEG400. Then a binary mixture of carrier (Avicel PH 102) and coating material (Cab-O-Sil M5) was prepared at a various ratio. This binary mixture was added to the admixture of drug and vehicle. From the reported Φ-value the liquid load factor (*Lf*) was calculated[12]. Depending upon the type of vehicle in the formulation, different liquid load factors were employed in liquisolid preparations. Different concentrations of Avicel and Cab-O-Sil M5 were used to prepare different liquisolid formulations. Finally, SSG as a disintegrant was added to the above powder blend and mixed. The final powder blend was subjected to compression. The important formulation characteristics of liquisolid compacts are shown in Table 1.

Precompression studies of the liquisolid system

Flow properties of the liquisolid system

The flow properties of the liquisolid systems were estimated by determining the angle of repose, Carr's index, and Hausner's ratio (table 2). The angle of repose was measured by the fixed funnel and freestanding cone method. The Bulk density and Tap densities were determined for the calculation of Hausner's ratio and Carr's Index[14].

In vitro evaluation of liquisolid compacts

Weight variation test

The weight variation test was performed as per USP[15] and results for all the batches of ATR liquisolid compacts are shown in Table 3.

Hardness and friability

The hardness of formulated liquisolid tablets was assessed using a Pfizer hardness tester, and the mean hardness of three tablets was determined. The friability of the prepared liquisolid tablets was measured in a Roche type apparatus and the percentage loss in weight was calculated and used as a measure of friability and the results for all the batches of IBS liquisolid compacts are shown in Table 3.

Disintegration test

The disintegration test was carried out using disintegration test apparatus as specified in the Indian Pharmacopoeia[16] and the results for all the batches of IBS liquisolid compacts are shown in Table 3.

Table 1: Formulation characteristic of prepared Irbesartan liquisolid Tablets

Liquisolid system	Liquid load factor (Lf)	Powder excipient ratio(R)	Avicel PH 101(Q)	Cab-O-Sil (q)	SSG	Mg stearate	Tablet weight
			Quantity in mg				
LS-1	0.402	9.5	248.75	26.12	29.32	6.12	310.31
LS-2	0.222	8.2	450.45	54.93	33.13	5.12	544.63
LS-3	0.557	9.1	179.53	19.59	28.30	4.19	231.61
LS-4	0.222	15.1	450.45	29.80	26.13	8.18	514.56
LS-5	0.222	5.1	450.45	88.45	27.13	8.98	575.01
LS-6	0.557	16.9	179.53	10.58	26.10	4.98	221.19
LS-7	0.402	6.7	248.75	37.07	23.14	6.32	315.28
LS-8	0.557	5.9	179.53	30.42	29.00	4.32	243.27
LS-9	0.402	16.6	248.75	14.98	27.2	5.69	296.58

Table 2: Physical properties of the prepared Irbesartan liquisolid powder

Liquisolid Powder	Angle of Repose	Densities (g/cm^3)		Hausner ratio	Carr's Index
		Bulk Density	Tap Density		
LS-1	36.19	0.315	0.509	1.42	29.90
LS-2	35.20	0.400	0.478	1.19	15.90
LS-3	33.13	0.300	0.475	1.29	19.35
LS-4	37.99	0.413	0.489	1.10	15.92
LS-5	35.50	0.395	0.409	1.29	21.85
LS-6	35.16	0.395	0.411	1.28	17.18
LS-7	34.16	0.428	0.426	1.20	15.97
LS-8	32.41	0.314	0.429	1.32	28.23
LS-9	38.24	0.297	0.418	1.47	30.19

Table 3: Quality control tests of Irbesartan tablets

Liquisolid tablets	Weight (mg)	Hardness (kg/cm^2)	Friability (g)	Disintegration (min)	Content Uniformity (%)
LS-1	310.31	4.3	0.013	5.03	96.2
LS-2	544.63	4.00	0.002	9.32	95.9
LS-3	231.61	3.90	0.019	7.23	100
LS-4	514.56	4.83	0.009	8.39	94.4
LS-5	575.01	5.90	0.25	11.43	98.3
LS-6	221.19	3.60	0.055	5.13	95.7
LS-7	315.28	4.78	0.024	6.07	99.6
LS-8	243.27	2.00	0.003	9.70	96.6
LS-9	296.58	4.26	0.006	2.14	100.7

In vitro dissolution studies

The *in-vitro* release profiles of IBS from liquisolid compacts and directly compressed tablets were obtained using a dissolution test apparatus USP-II (Electro Lab). The dissolution study was carried out in 900 ml 0.1 N HCl and as the dissolution medium at 37˚C ± 2˚C and 75 rpm. Then 5 ml samples were collected for up to 60 min at 5-min intervals up to 30 min and 15 min intervals from 30 to 60 min. The dissolution medium was replaced with 5 ml fresh dissolution fluid to maintain sink conditions. The withdrawn samples were filtered and analyzed spectrophotometrically (1700, Shimadzu, Japan) at 244 nm. The mean of three determinations was used to calculate the drug release from each of the formulations.

RESULTS AND DISCUSSION

Solubility and UV analysis of IBS

IBS was selected as the model drug for these studies since it is a very poorly water soluble drug and a suitable candidate for testing the potential of rapid release liquisolid compacts. All the standard curves of IBS solutions obeyed Beer's law which was linear over the concentration range tested from 5–50 µg/ml. The solubility in distilled water and polyethylene glycol was found to be 0.0543 ± 0.043% (w/w), 12.09% ± 0.365% (w/w) respectively.

Application of a mathematical model in designing the IBS liquisolid system

To calculate the required ingredient quantities, the flowable liquid-retention potentials (Φ-values) of powder excipients were used. According to S. S. Spireas *et al* [15] in PEG 400, the Φ-value was 0.005 for Avicel PH 102 and 3.26 for Cab-O-Sil M5. The liquid load factor was computed from the flowable liquid-retention potential in accordance with equation 3 using a different *R* value (excipient ratio). The most suitable quantities of carrier (*Q*) were calculated using equation 2. The optimum quantities of carrier (*Q*0) and coating material (*q*0) were obtained from equation 4 and 5 respectively.

Precompression studies of the liquisolid system

Flow properties of the IBS liquisolid system

The flow properties of the liquisolid powder system are influenced by physical, mechanical as well as environmental factors. Therefore, different flow parameters were employed. As the angle of repose (θ) is a characteristic of the internal friction or cohesion of the particles, the value of the angle of repose will be high if the powder is cohesive and low if the powder is non-cohesive. LS-1 shows good flow properties with a θ value of 28.61 and is considered as a All the formula of liquisolid system shows acceptable flowability. Carr's

index up to 16 was considered acceptable as a flow property. Hausner's ratio was related to the inter particle friction; powders with a low interparticle friction had a ratio of approximately 1.25 indicating a good flow. The LS-2 and LS-4 system with a Carr's index of 15.90 and 15.92 respectively.

It was found that, there is a relationship between powder excipient ratios (R) and the angle of repose of the liquisolid powders in the formulae having the same L_f. The powder excipient ratio (R) was directly proportional to the angle of repose of the liquisolid powders i.e., when the powder excipient ratio (R) increased the angle of repose of the liquisolid powders will increase. This was observed from the following results: formulae LS-8, LS-3, and LS-6 were having the same L_f equal to 0.557and (R) 5.9, 9.16, and 16.96, respectively, and the mean angle of repose of the liquisolid powders were 32.41, 33.13, and 35.16 degrees, respectively. And this finding was confirmed by the third example, formulae LS-7, LS-1, and LS-9 having L_f 0.402 and the mean angle of repose of the liquisolid powders of them were 34.6, 36.19, and 38.24 degrees, respectively. This can be explained by the fact that, increasing (R) of the formula leading to increase in the amount of the carrier powder used (Avicel PH 101) which is a highly porous material and decrease the amount of the coating material "Cab-O-Sil", which is a very fine particle size silica powder responsible for the flowability of the powder, and this subsequently, lead to the increase of the angle of repose of the powder.

In vitro evaluation of liquisolid compacts

It was clear from Table 3, that all the investigated liquisolid tablets complied with the pharmacopoeial requirements as regard their content uniformity, which was found to lie within the range 95-105%.

Hardness, Friability, Weight variation, Disintegration test

Table 3 showed the uniformity of weight of all investigated tablets. Most Pharmacopoeias include a simple weight test on a specified number of tablets, which are weighed individually, and the arithmetic mean weights calculated. The permitted weight variations in USP, not more than two tablets differ from the mean by more than5%, and none of the investigated tablets differ from the mean by more than 10%. In B.P., the permitted weight variations are essentially the same as that of the USP. It was clear from the obtained results that all the investigated all tablets met with the requirements of USP and BP.

The mean of the hardness of values of tablets were shown in Table 3. The Optimum hardness for each liquisolid tablet was calculated according to (Spireas,2002) as follow: specific crushing strength of a tablet is the ratio of its crushing strength (hardness) over its weight, for instance, liquisolid tablets weighing 0.6 and 0.3 grams were compressed to hardness of 9 kg (i.e., 15 kg/0.6g) and 4.5 kg (i.e., 15kg/0.3g), respectively. It was found that LS-3had the worst hardness and the largest deviation from the mean.

It was found that, there is a relationship between liquid load factor (L_f) and the hardness of the tablets in the formulae having approximately the same powder excipient ratio. The liquid load factor was inversely proportional to the hardness of the tablets i.e., when the L_f increased the hardness of the tablets will decrease, and this was obvious from the following results. Formulae LS-5, LS-7, and LS-8 were having L_f 0.222, 0.402, and 0.557, and the mean hardness of them was 5.9, 4.78, and 2.0 kg, respectively. Also, Formulae LS-1, LS-2, and LS-3 having L_f 0.222, 0.402, and 0.557, and the mean hardness of them were 4.3, 4.0, and 3.90 kg, respectively. And this finding was confirmed by the third example, formulae LS-4, LS-9, and LS-6 having L_f 0.222, 0.402, and 0.557, and the mean hardness of them were 4.83, 4.26, and 3.60 kg, respectively. This can be explained by that, increasing L_f of the formula increasing the amount of solvent used and decreasing the amount of powder excipient and this subsequently, decrease the hardness of the tablets.

Another finding was declared from the obtained data that there is a relationship between powder excipient ratios(R) and the hardness of the tablets in the formulae having the same L_f. The powder excipient ratio (R) was inversely proportional to the hardness of the tablets i.e., when the powder excipient ratio (R) increased the hardness of the tablets will decrease; this finding was cleared from the table. This can be explained by that, increasing (R) of the formula there by increase the amount of the carrier powder (Avicel PH 101)used which is a highly porous material and the amount of the coating material "Cab-O-Sil" will decreased and this subsequently, lead the tablet to be friable and decreased the hardness of the tablets.

All the batch of liquisolid tablets of IBS complies the friability test since all the results fall within friability limits.

The disintegration time for the prepared IBS liquisolid tablets was shown in Table 3. It was found that, the mean of the disintegration times for all investigated tablets were less than 30 minutes, which fulfill the Pharmacopoeial requirements. LS-9 was showed less disintegration time (2.14 minutes). While, the slowest disintegrated formula was LS-5, which toke 11.43 minutes to disintegrate.

The same finding was obtained from the results of the investigation of the disintegration time of the tablets. It was found that, there is a relationship between liquid load factor (L_f) and the disintegration time of the tablets in the formulae having approximately the same powder excipient ratio. The liquid load factor was inversely proportional to the disintegration time of the tablets i.e., When the Lf increased the disintegration time of the tablets will decrease, and this was clearly shown from Table 3. That, increasing L_f of the formula increasing the amount of liquid used and significantly increased wetting properties and surface area of the drug and increasing the

availability of the drug to be easily disintegrated from its solution or suspension, and this subsequently; decrease the disintegration time of the tablets, can explain this finding.

Another finding was displayed from the obtained results that there is a relationship between powder excipient ratios (R) and the disintegration time of the tablets in the formulae having the same Lf. The powder excipient ratio (R) was inversely proportional to the disintegration time of the tablets i.e., when the powder excipient ratio (R) increased the disintegration time of the tablets will decreased, this finding was cleared from the results depicted in table 3. This can be explained by that, increasing (R) of the formula leading to the high microcrystalline cellulose content where Avicel PH 101 functions as a swellable disintegrant (Patel et al, 1994). In addition, the highly hydrophilic characteristic of microcrystalline cellulose could increase the wetting of IBS and this subsequently, lead the tablet to be disintegrated quickly and decreased the disintegration time of the tablets[17].

In-vitro release of Irbesartan from liquisolid tablets

Fig.1 shows the dissolution profile of LS system and DC compacts of IBS. Liquisolid compacts displayed more distinct *in-vitro* release characteristics than their directly compressed counterparts. The percentage drug release at the end of the 60th min was 96.48% for LS-6 and 49.41% for DC. It was confirmed that at 10 min LS-1 had the highest drug release 65.28% compared with 17.19% for the directly compressed compact (DC).

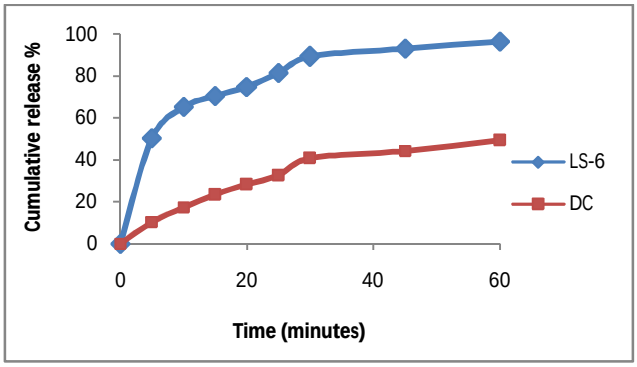

Figure 1: Dissolution profile of LS-1 ans DC.

Since the liquisolid compacts contain a solution of the drug in non volatile vehicle used for preparation of the liquisolid compacts, the drug surface available for dissolution is tremendously increased. In essence, after disintegration, the liquisolid primary particles suspended in the dissolving medium contain the drug in a molecularly dispersed state, whereas the directly compressed compacts are merely exposed micronized drug particles. Therefore, in the case of liquisolid compacts, the surface area of drug available for dissolution is much greater than that of the directly compressed compacts. From the obtained results, it was displayed that there is a relationship between the powder excipient ratio and the invitro release of Irbesartan from liquisolid tablets. The powder excipient ratio was directly proportional to the invitro release i.e., when the powder excipient ratio increased the release will increase. This finding was declared from the following results. Formulae LS-8, LS-3, and LS-6 were having the same Lf equal to 0.557 and had(R) equal to 5.90, 9.16, and 16.96, and the cumulative percent released were 90.20, 93.66, and 96.48%, respectively. This may be attributed to the high microcrystalline cellulose content where Avicel PH 101 functions as a swellable disintegrant[18]. In addition, the highly hydrophilic characteristic of microcrystalline cellulose could increase the wetting of IBS and enhance its dissolution[19].

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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