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FORMULATION AND EVALUATION OF RAPID RELEASE SYSTEM OF IRBESARTAN BY LIQUISOLID TECHNOLOGY

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ABSTRACT

The oral route is still the most popular way to administer drugs since it is convenient, patient compliance is high, and the cost of producing medicine is low. A medication needs to dissolve in the stomach juices in order to be absorbed into the systemic circulation after oral delivery. Poor solubility is thus one of the main obstacles facing medication development today. The solubility and dissolution rate of hydrophobic medicines, which are classified as class II in the biopharmaceutics categorization system, limit their bioavailability. Reducing particle size, reducing crystallinity, and/or increasing surface area can all help these medications dissolve more quickly. Numerous investigations have been conducted in an effort to produce nanoparticles and microparticles, which reduce particle size and speed up the dissolving of medications. However, due to the presence of the residual solvent in the drug formulation, it is disadvantageous to use toxic solvents. To overcome the problem, the technique of “liquisolid compacts” is a new and promising approach towards dissolution enhancement Liquisolid compacts possess acceptable flowability and compressibility properties. The *in vitro* release studies revealed that the liquisolid tablets showed a faster drug release compared to the conventional tablets.

Keywords: Solubility, tablet, liquisolid, dissolution, microparticles

1 INTRODUCTION

Numerous methods are being used to improve the solubility of poorly soluble medications in order to address the problem of insufficient dissolving rate-related bioavailability. Hydrophilic polymers are used in several ways as solubility enhancers, working via a range of mechanisms such inclusion complexes, co-solvency, micelle formation, and amorphization. These methods have numerous beneficial benefits on the formulation development process. However, over time, these methods typically exhibit a lack of stability and a declining success rate. A notable drawback of inclusion complexes, glass solutions, eutectic mixes, and solid dispersions is the development of a sticky and hygroscopic mass that impairs flow properties. The emergence of a novel drug delivery method that can deliver a wide range of medications is attributed to the liquisolid technology. Pharmaceutical researchers are paying more attention to liquidsolid drug delivery systems because they can be used to improve solubility or delay dissolution, depending on the formulation's needs and design. By using specific excipients and easy physical blending, a liquid can be turned into a free-flowing, easily compressible, and seemingly dry powder using Spireas's patented liquisolid technique. Liquisolid compacts are made up of three main ingredients: coat material, carrier, and liquid drug. Other excipients are utilized in accordance with the goal and requirements of the formulation, such as the use of disintegrants or release-delaying polymers to modify the release profile. The first ingredient, the liquid medication, can be any of the following: a liquid drug in appropriate non-volatile liquid carriers, a liquid drug suspension, or a liquid drug solution. The ideal "liquid vehicle" would be an inert organic solvent system with a high boiling point, particularly one that is water soluble, like

glycerin, propylene glycol, or liquid polyethylene glycols. The medication remains evenly and molecularly disseminated when it is dissolved in a non-volatile solvent. This offers the chance to improve the medication release. The second part of the system, the porous carrier material, is integrated with the liquid medication. A liquid layer forms on the particle surface after the carrier is saturated with liquid, and the third component—the coat materials—adsorbs this layer right away. The coat substance, which makes up the third component, prevents the liquisolid particles from re-aggregating and improves flow properties. The coating also contributes to the system's seeming dryness. Amorphous silicon dioxide, often known as colloidal silica, is frequently utilized as a coating material. Higher surface area of the drug available for release, increased aqueous solubility of the drug by co-solvency, and improved wettability of the drug particles are the reasons for enhanced drug release in a liquidsolid formulation containing a drug solution or drug suspension of poorly soluble drugs in a solubilizing vehicle. As a result, this enhanced drug release could lead to increased drug absorption in the gastrointestinal system and, consequently, enhanced oral bioavailability.[1,2]

1.1 Mechanisms of Enhanced Drug Release from Liquisolid Systems

For liquisolid systems, many strategies of increased drug release have been proposed. Three key processes have been proposed: an increase in the drug's surface area available for release; an increase in the drug's aqueous solubility; and an improvement in the drug particles' wettability[3,4].

1.2 Increased Drug Surface Area

The drug is found in the powder substrate in a solubilized, molecularly distributed condition if it is fully dissolved in the liquid vehicle within the liquisolid system. As a result, compared to the drug particles inside directly crushed tablets, the drug's surface area available for release is significantly larger.when a result, the release rate reduces when the drug content rises above the solubility limit and the proportion of undissolved drug in the liquid vehicle rises as well.

With various drugs, it could be shown that the release rates are directly proportional to the fraction of the molecularly dispersed drug (*FM*) in the liquid formulation. *FM* is defined by the ratio between the drug's solubility (*Sd*) in the liquid vehicle and the actual drug concentration (*Cd*) in this vehicle carried by each system. Therefore

$$F\,M = Sd / Cd$$

Where $FM = 1$ if $Sd \geq Cd$

Accordingly, lower *FM*-values and higher fraction of undissolved drug in the liquid vehicle, respectively, are not sufficient to increase percentage of drug released at 30 min. However, this may not be transferred to other time points of drug release[5].

1.3 Increased aqueous Solubility of The Drug

In addition to the first mechanism of drug release enhancement it is expected that *Cs*, the solubility of the drug, might be increased with liquisolid systems. In fact, the relatively small amount of liquid vehicle in a liquisolid tablets is not sufficient to increase the overall solubility of the drug in the aqueous dissolution medium. However, at the solid/liquid interface between an individual liquisolid primary particle and the release medium it is possible that in this microenvironment the amount of liquid vehicle diffusing out of a single liquisolid particle together with the drug molecules might be sufficient to increase the aqueous solubility of the drug if the liquid vehicle acts as a co-solvent. The overall increase in the solubility of drugs caused by liquisolid systems was confirmed[6,7].

1.4 Improved Wetting Properties

Due to the fact that the liquid vehicle can either act as surface active agent or has a low surface tension, wetting of the liquisolid primary particles is improved. Wettability of these systems has been demonstrated by measurement of contact angles and water rising times[8]

2 MATERIALS REQUIRED FOR FORMULATION

Liquisolid system mainly includes:

- Drug candidate
- Non volatile solvent
- Disintegrant
- Carrier material
- Coating material

2.1 Drug Candidate

These are poorly soluble or else insoluble drugs in water.

2.2 Non-Volatile Solvent

Non-volatile Solvent should be inert, high boiling point, preferably water- miscible and not highly viscous organic solvent systems and compatible with having ability to solubilise the drug. The non volatile solvent acts as a binding agent in the liquisolid formulation. Various non-volatile solvents used for the formulation of liquisolid tablets includes Polyethylene glycol400, Propylene glycol, Polysorbate 80, Capryol 90.

2.3 Selection of Solvent

Drug solubility tests were conducted in a variety of non-volatile liquid vehicles in order to determine which non-volatile solvent would work best for suspending or dissolving the drug in liquid medication. Excess medication was added to the liquid vehicles to create saturated solutions, which were then continuously stirred and shaken at 25°C for 48 hours. Following this time frame, the solutions were passed through a 0.45 µm millipore filter, diluted with distilled water, and then subjected to an analysis at a designated wavelength using a UV spectrophotometer against a blank sample (a blank sample that had the same concentration of the particular solvent employed without the drug).

To determine the drug's solubility, each sample underwent three determinations. Liquisolid tablets can be made using some of the solvents listed above, such as propylene glycol, polyethylene glycol (PEG 200, 400, 600), castor oil, capryol 90, poloxamer 181, polyoxyl 35, and Spans. The solvent must possess the qualities of being non-volatile and non-toxic. The choice of solvent and the characteristics of the chemical entities determine whether the formulation of liquisolid compacts will accelerate or slow down the drug's rate of dissolution. Checking the saturation solubility with a few chosen non-volatile solvents is necessary before choosing a solvent for the formulation. [9,10].

2.4 Disintegrant

Super disintegrants increases the rate of drug release, water solubility and wettability of liquisolid granules. Mostly superdisintigrants like sodium starch glycolate, croscarmelose sodium, pre gelatinized starch and crosspovidone are used.

2.5 Carrier Materials

Porous material with adequate absorption qualities that aid in liquid absorption should be used as the carrier material. Because the coating and carrier materials can only hold so much liquid while still maintaining suitable flow and compression characteristics, raising the moisture level of the carrier reduces the powder's flowability. As carrier materials, lactose and many grades of microcrystalline cellulose, including Avicel PH 102, PH 200, and experimental grade of granular amorphous cellulose, are utilized [11].

2.6 Coating Materials

The ideal coating material has small, highly adsorptive particles that help cover the wet carrier particles and provide the appearance of a dry powder by adsorbing extra liquid. To cover the surface and keep the powder flowable, coating material is needed.

3 EXPERIMENTAL DETAILS

3.1 Solubility Studies

Irbesartan solubility tests are conducted in Tween 80, PEG-600, Tween -20, propylene glycol, and polyethylene glycol 400 (PEG 400). To prepare saturated solutions, add more medication to the vehicles and shake continuously for 48 hours at 25 ± 0.5 0C on a shaker. Following this time, the solutions are diluted, filtered, and UV spectrophotometer-analyzed. To determine how soluble irbesartan is in each sample, three calculations are made. Based on the findings, it was noted that the drug's solubility in propylene glycol was greater than that of other liquid vehicles.[12]

3.2 Procedure for Preparation of Liquisolid System

Several irbesartan liquisolid formulations are prepared in different drug concentration. Each formulation contains Avicel PH200 as carrier and Aerosil 200 as coating material, at carrier/coat ratio (R value) of 15 ,20 and 25. The appropriate amounts of carrier and coating materials used for each formulation depend upon Lf of that formulation. The ΦCa and ΦC_0 values for particular liquid vehicle are used to calculate Lf [Eq- (1)] of that respective liquid vehicle. Once the liquid load factor (Lf) and amount of liquid medication (W) are determined, amount of carrier (Q) and coating (q) can be calculated by rearranging Eq- (2) and (3).

$$Lf = \Phi Ca + \Phi C_0 \times 1/R \quad \text{---------- (1)}$$

$$Lf = W/Q \quad \text{---------- (2)}$$

$$R = Q/q \quad \text{---------- (3)}$$

The drug-vehicle liquid system is produced by mixing irbesartan in non-volatile liquid vehicle using a mortar and pestle. To this liquid medication, the calculated amount of the carrier (Avicel PH200) is added by continuous mixing in the mortar. Then the coating material (Aerosil 200) is carefully added and mixed until mortar contents start to look like dry powder. In the last stage of the preparation, a 5% (w/w) sodium starch glycolate as a super disintegrant and 0.75% (w/w) of magnesium stearate as a lubricant are added and mixed. All liquisolid preparations are compacted into tablets using a single punch tablet machine having 10mm flat punch[13,14].

3.3 Precompressional Evaluation of Powder Blend

Powder flow is a critical character that might affect uniformity of the tablet weight. Therefore, the flow properties of the powder blend of all liquisolid formulations were determined[15,16].

3.4 Postcompressional Evaluation of Liquisolid Tablets

Tablets of different formulations were evaluated for the postcompressional parameters such as weight variation, hardness, thickness, friability, disintegration time and drug content for tablets[17,18]

Table-1: Composition of irbesartan liquisolid tablet

code	R	Drug (mg)	Liq-uid vehic-le(mg)	Lf	Avicel PH200 (Q) (mg)	Aerosil 200 q (mg)	Disint egrant [SSG] (mg)	Magst earate (mg)	Wt of tab. (mg)
F1	5	50	50	0.822	121.65	24.2	17.25	2.6	265.7
F2	10	50	50	0.491	203.66	20.3	16.15	2.4	342.51
F3	15	50	50	0.380	263.15	17.53	19.05	2.8	401.98
F4	20	50	50	0.325	307.69	15.38	21.1	3.1	446.58
F5	25	50	50	0.292	342.46	13.69	22.75	3.4	481.84
F6	30	50	50	0.270	370.37	12.34	24.1	3.6	510.04

Table-2: Precompressional evaluation of powder blend

Formulation code	Angle of repose θ ± SD*	Bulk density (g/ml) ± SD*	Tapped density (g/ml) ± SD*	Car's index (%) ± SD*	Hausner's ratio ± SD*
F1	28.96 ±0.74	0.206 ±0.01	0.250 ±0.00	17.57 ±2.12	1.20± 0.03
F2	27.92 ±0.79	0.324 ±0.01	0.367 ±0.02	11.84 ±0.60	1.13± 0.01
F3	28.18 ±1.02	0.644 ±0.00	0.782 ±0.00	17.63 ±0.06	1.21± 0.00
F4	29.39 ±0.80	0.495 ±0.03	0.604 ±0.04	18.05 ±1.19	1.22± 0.00
F5	28.93 ±0.68	0.515 ±0.01	0.640 ±0.02	19.54 ±0.77	1.23± 0.01
F6	25.00 ±0.25	0.825 ±0.03	0.916 ±0.00	9.96± 1.44	1.11± 0.01

Table-3: post compressional evaluation of liquisolid tablets

Formulation code	Hardness (kg/cm2)	Thickness (mm)	Weight variation (mg)	Friability (%)	Disintegration Time(sec)	Drug content (%)± sd*
F1	4	2.52	265.1 .±.1.87	0.44	6 min 27 sec	98.95± 0.35
F2	4	3.21	42.19±2. 44	0.17	6 min 14 sec	98.10± 0.35
F3	5	3.41	401.7 ±1.81	0.19	5 min 40 sec	97.64± 045.
F4	5	2.45	446.21± 2.96	0.11	4 min 33 sec	98.65± 0.35
F5	5	2.58	481.58± 2.28	0.4	4 min 12 sec	98.53± 0.80
F6	5	4.92	510.42± 3.22	0.16	3 min 10 sec	99.92± 0.53

3.4 *In Vitro* Release Studies

In vitro release studies is performed by using USP type II Paddle dissolution apparatus in 900 ml of distilled water maintained at 37° C ± 0.5° C and rotation speed of 50 rpm. Samples (5 ml) are withdrawn at suitable time intervals (5, 10, 15, 20, 25, 30, 45, 60 minutes) and filtered through whatman filter paper. Sink conditions are maintained throughout the study. The withdrawn samples are analyzed by UV- visible spectrophotometer (Shimadzu UV-1700 pharma spec, Japan) at λ_{max} of 224nm. The studies are done in triplicate[19,20]

Table-4: *In vitro release study*

Time (min.)	Cumulative percentage drug release ± sd*					
	F1	F2	F3	F4	F5	F6
5	31.97 ±0.63	30.70 ±1.26	34.08 ±0.36	32.39 ±0.36	38.93 ±0.63	26.91 ±0.63
10	42.77 ±0.63	42.14 ±0.63	44.67 ±0.63	42.56 ±0.36	46.99 ±0.96	48.76 ±0.36
15	49.97 ±0.63	48.28 ±0.36	49.98 ±0.63	48.49 ±0.36	54.42 ±0.63	45.94 ±0.96
20	61.01 ±0.63	60.15 ±0.96	62.91 ±0.63	60.57 ±0.36	64.85 ±0.63	67.37 ±0.97
25	69.15 ±0.97	67.23 ±0.37	69.80 ±0.36	68.29 ±0.63	72.59 ±0.97	76.34 ±1.27
30	77.54 ±0.64	75.19 ±0.37	78.20 ±1.68	75.42 ±0.36	79.53 ±0.64	83.03 ±0.65
45	86.83 ±0.64	84.89 ±0.64	88.97 ±1.33	87.01 ±0.97	91.99 ±1.28	92.93 ±1.28
60	90.79 ±0.65	91.48 ±0.64	99.28 ±0.35	94.24 ±0.62	96.64 ±0.35	99.64 ±0.99
Con-vential tablet	8.76 ±0.36	11.97 ±0.36	15.41 ±0.36	17.61 ±0.630	21.50 ±0.63	35.20 ±0.64

4 CONCLUSIONS

The purpose of the study was to formulate liquisolid tablets of irbesartan to improve the solubility and dissolution rate. The solubility studies were observed that the irbesartan have highest solubility in propylene glycol compared to other non-volatile liquid vehicles. The results of precompression studies which indicates that the prepared powder blend of all the formulations possess good flow properties.The post compression evaluations such as hardness, thickness, weight variation, friability, drug content and disintegration test of all the formulated liquisolid tablets were within the acceptable limits. *In vitro* dissolution studies of all the formulations showed immediate release of drug..The *in vitro* release studies revealed that the liquisolid tablets showed a faster drug release compared to the conventional tablets. The liquisolid tablet technique can be effective way for dissolution rate improvement of water insoluble drugs such as irbesartan. This novel approach to the formulation will be helpful to improve oral bioavailability.

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