Research Article

Formulation and Evaluation of Liquisolid Compacts of Zotepine

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ABSTRACT

The aim of present research work is to formulation and evaluates Liquisolid Compacts of Zotepine to improve solubility and dissolution rate of drug. Solubility and dissolution rate of Zotepine was increased by preparing Liquisolid Compacts of Zotepine using PEG as vehicle, Aerosil as coating agent and Avicel as adsorbent and sodium starch glycolate as super disintegrant. FTIR study was checked for possible drug excipient interaction. The hardness of all formulation was found good enough to pass the friability criteria. Hence the friability of the formulation is well within the acceptance criteria. The friability was found less than 1 in all formulations. Further, the drug content of the formulation batches F1-F8 found within acceptance range. The disintegration time of the F1-F8 batches was found less the 60 seconds. It was found that the amount of SSG is directly affecting to DT time of formulation. The F8 formulation was found stable for 1 month during stability study. Liquisolid Compacts of Zotepine were successfully developed by using PEG as vehicle, Aerosil as coating agent and Avicel as adsorbent and sodium starch glycolate as super disintegrant.

Keywords: Zotepine, Liquisolid Compacts, formulation, evaluation.

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INTRODUCTION

Liquisolid technique is a new and promising method that can change the dissolution rate of drugs. It has been used to enhance dissolution rate of poorly water-soluble drugs. For poorly soluble (Class II) drugs and class (Class IV) the rate of oral absorption is often controlled by the dissolution rate in the gastrointestinal tract.[1-2] The new 'liquisolid'' technique may be applied to formulate liquid medications (i.e., oily liquid drugs and solutions, suspensions or emulsions of water insoluble solid drugs carried in nonvolatile liquid vehicles) into powders suitable for tableting or encapsulation. Since, the liquisolid tablets contain a solution of the drug in suitable solvent; the drug surface available for dissolution is tremendously increased. Due to significantly increased wetting properties and surface area of drug available for dissolution, liquisolid compacts of water-insoluble substances may be expected to display enhanced drug release characteristics and, consequently, improved oral bioavailability. In this case, even though the drug is in a solid dosage form, it is held within the powder substrate in solution or, in a solubilize, almost molecularly dispersed state, which contributes to the enhanced drug dissolution properties.[3-6] Based on the type of liquid medication contained therein, liquisolid systems may be classified into three subgroups:

1) Powdered drug solutions 2) Powdered drug suspensions 3) Powdered liquid drugs

The first two may be produced from the conversion of drug solutions or (e. g. prednisolone solution in propylene glycol) or drug suspensions (e. g. gemfibrozil suspension in Polysorbate 80), and the latter from the formulation of liquid drugs (e. g. clofibrate, valproic acid, liquid vitamins, etc.), into liquisolid systems. Based on the formulation technique used, liquisolid systems may be classified into two categories, namely

1) Liquisolid compacts 2) Liquisolid Microsystems

Liquisolid compacts are prepared using the previously outlined method to produce tablets or capsules, whereas the liquisolid Microsystems are based on a new concept which to produce an acceptably flowing admixture for encapsulations.[7-10]

MATERIALS

Zotepine was obtained as a gift sample from Astron, Ahmedabad, Microcrystalline cellulose (MCC) (Avicel PH 102), Aerosil 200, Sodium starch glycolate, Polyethylene glycol 400 wasobtained from Balaji Chemicals, Ahmedabad.

METHODS

Solubility Study

The Solubility study was performed using nonvolatile solvent. Drug was dissolved in that solvent and saturated solutions were prepared. Prepared solution was analyzed by UV spectrophotometer at 265 nm. Selection of non-

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volatile solvent is most important for the preparation of liquisolid compacts.

Preparation of Zotepine Liquisolid Compacts

Selection of Vehicle

Initially drug solubility was checked in different solvents. Solubility of a drug in a nonvolatile vehicle is one of the most important key parameter for the preparation of liquisolid compacts. Improvement in solubility directly affects the dissolution rate. Finally according to solubility data of drug, PEG 400 was selected as the vehicle for further study.

Liquid load factor

Liquid Loading factor was calculated for carriers and for the non-volatile solvent system.

Lf (Liquid Loading factor) = W/Q

Where, W: Amount of liquid medication

Q: Amount of carrier material

Manufacturing Method

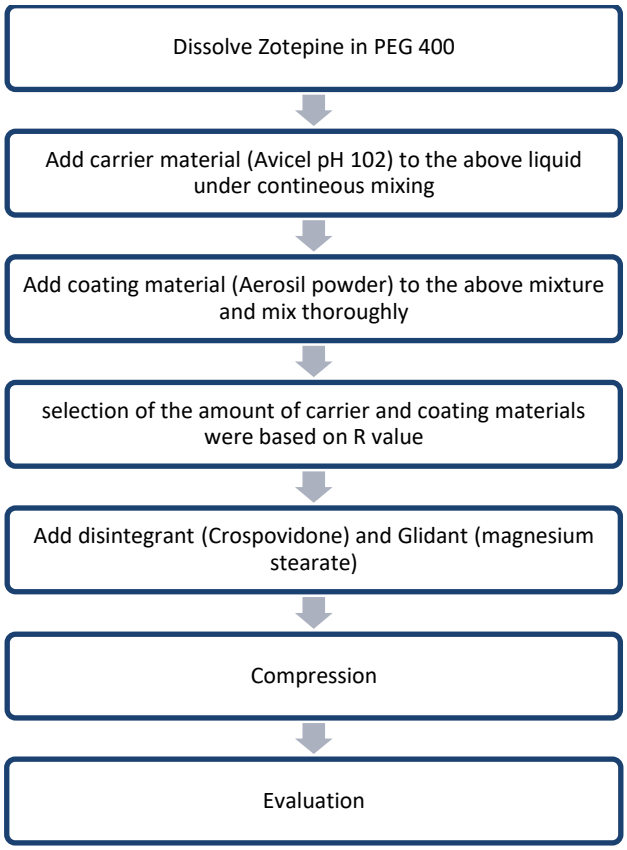

Table 1: Formulation of Zotepine Liquisolid Compacts

Batch	Zotepine (mg)	R (R=Q/q)	Carrier Avicel pH 102 (Q=W/Lf)	Coating (mg) Aerosil (q=Q/R)	Liquid Vehicle (mg)	Loading Factor (Lf=W/Q)	Weight (mg)
F1	25	5	200	40	15	0.200	294.0
F2	25	5	210	42	17	0.200	308.7
F3	25	5	220	44	19	0.200	323.4
F4	25	5	230	46	21	0.200	338.1
F5	25	10	350	35	15	0.114	446.2
F6	25	10	360	36	16	0.114	458.8
F7	25	10	370	37	17	0.114	471.4
F8	25	10	380	38	18	0.114	484.1

- *SSG was added 5% of total weight*

Excipient ratio, R=Q/q

Q- Weight of carrier;

q- Weight of coating material.

Liquid load factor, Lf = W/Q

W- Weight of liquid medication.

Carrier amount Q=W/Lf

Evaluation of Zotepine Liquisolid Compacts

Pre compression parameters

Bulk density

The bulk density in gm/ml was calculated by using the following formula.

Bulk density = Weight of the powder/Bulk volume of Powder

Tapped density

The tapped density in gm/ml was calculated by using the following formula.

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Tapped density= Weight of powder taken/ Tapped Volume

Compressibility index

The Compressibility index was calculated using following formula;

Compressibility index (%) = ρt – ρo* 100 / ρt

Where ρt = Tapped density gram/ml, ρo = Bulk density gram/ml.

Hausner's ratio

Hausner's ratio= Tapped density/ Bulk density

Angle of repose

Funnel method was used to measure angle of repose. Angle of repose is calculated using the following equation;

tan= θ h/r

Where, h and r are the height and radius of the powder cone.

Post-compression parameters

Weight variation

Accurately weight 20 tablets individually using electronic weighing balance and calculate the average weight of tablets and calculate standard deviation.

Thickness

The digital vernier caliper was used to check the thickness of the tablets. The test is performed in triplicate. Average of the three-reading reported and standard deviation calculated.

Hardness test

The hardness of the tablets was tested by using Monsanto tester. The parameter was checked in triplicate.

Friability test

The friability of the tablets was determined using Roche friabilator. The % friability calculated based on following formula:

Friability= ([W –W]/WO) *100

Where, Wo =initial weight of tablet; W = after test weight of tablet.

In-vitro *disintegration test*

The test was carried out on 6 tablets using tablet disintegration tester. Water at 37 ± 2˚C was used as a disintegration media and the time taken for complete disintegration of the tablet was noted with no passable mass remaining in the apparatus was measured.

Drug content

Ten tablets were selected randomly and average weight was calculated. Tablets were crushed in a mortar and accurately weighed amount of tablet powder was taken from the crushed blend and transferred it in to a 100 ml volumetric flask.10 ml of 0.1 N HCl was added and sonicated for 10 minutes. Then volume was made up to 100 ml with 0.1 N HCl. The 1mL of resultant solution was diluted to 100mL with buffer (pH 1.2). The absorbance of above solution was measured in UV spectrophotometer at 265 nm.

Dissolution studies

The drug release from liquisolid tablets was studied using USP II Dissolution Testing Apparatus. The dissolution test was performed using 900 ml of 0.1 N HCl pH 1.2, at 37 ± 0.5°C and 50 rpm. Sample around 2 ml withdrawn from the dissolution apparatus at different time intervals like 0, 5, 10, 15, 25, 35, 45 minutes intervals. The samples were filtered and checked in UV.

Stability studies

Stability study will be performed as per ICH guideline for short term period of 1 month. The final optimized formulation will be kept at 40˚C and 75% RH condition for 1 month and evaluated for hardness, % drug content, and disintegration time and % drug release.

RESULTS AND DISCUSSION

Solubility Study of Drug

Solubility study of Zotepine was performed using nonvolatile solvents and the results were reported below. The selection of non-volatile solvent is most important factor in liquisolid compacts. Based on the solubility data, the highest solubility of drug found in PEG 400 as compared to other solvents. Hence PEG 400 was selected as a vehicle for preparation of liquisolid compacts.

Table 2: Solubility of Zotepine in non-volatile solvents

Sr. No.	Solvent	Solubility (mg/ml)
1	Glycerin	1.2
2	Propylene Glycol	3.6
3	Polysorbate 80	1.8
4	PEG 200	2.9
5	PEG 400	6.7

Evaluation of Liquisolid Compacts

Pre Compression Parameters

Formulation F1-F8 Liquisolid compact tablets evaluated for pre compression parameters and results are recorded in table which are given below table 3

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Table 3: Pre compression parameters of F1-F8

Batch	Bulk Density (gm/ml) (n=3)	Tapped Density (gm/ml) (n=3)	Compressibility Index % (n=3)	Hausner Ratio	Angle of Repose (θ)
F1	0.520 ± 0.04	0.655 ± 0.06	20.61	1.26	42°56’
F2	0.525 ± 0.03	0.675 ± 0.07	22.22	1.29	44°72’
F3	0.518 ± 0.02	0.671 ± 0.05	22.80	1.30	45°60’
F4	0.530 ± 0.05	0.666 ± 0.08	20.42	1.26	40°10’
F5	0.525 ± 0.07	0.675 ± 0.07	22.22	1.29	42°38’
F6	0.515 ± 0.05	0.655 ± 0.06	21.37	1.27	43°48’
F7	0.523 ± 0.04	0.653 ± 0.05	19.91	1.25	39°89’
F8	0.535 ± 0.03	0.630 ± 0.04	15.08	1.18	32°32’

From the above data it concluded that all the formulations have good Compressibility overall the flow properties was found satisfactory and expected. The data are suitable for the direct compression method and easy of flow during compression.

Post Compression Parameters

Formulation F1-F8 Liquisolid compact tablets evaluated for post compression parameters like weight variation, thickness, diameter, hardness, friability, drug content and drug release. The results are recorded in table which are given below table 4 & 5

Table 4: Post compression parameters of F1-F8

Formulation	Weight Variation (mg) (n=20)	Thickness (mm) (n=3)	Diameter (mm) (n=3)
F1	294.0 ± 2.6	3.45 ± 0.03	12.5 ± 0.1
F2	308.7 ± 3.8	3.58 ± 0.08	12.5 ± 0.1
F3	323.4 ± 2.9	3.67 ± 0.07	12.5 ± 0.1
F4	338.1 ± 2.5	3.74 ± 0.05	12.5 ± 0.1
F5	446.2 ± 4.1	4.12 ± 0.07	12.5 ± 0.1
F6	458.8 ± 3.9	4.23 ± 0.06	12.5 ± 0.1
F7	471.4 ± 3.5	4.56 ± 0.09	12.5 ± 0.1
F8	484.1 ± 3.3	4.76 ± 0.07	12.5 ± 0.1

The weight variation was found well within acceptance limit. Further, the thickness is found uniform and the diameter is also found uniform.

Table 5. Post compression parameters of F1-F8

Formulation	Hardness (kg/cm²) (n=3)	Friability %	Drug Content (%) (n=3)	Disintegration time (Sec) (n=3)
F1	4.9 ± 0.5	0.26	97.9 ± 1.5	39 ± 3
F2	4.9 ± 0.4	0.30	98.1 ± 2.2	35 ± 2
F3	4.7 ± 0.6	0.38	99.5 ± 1.3	30 ± 5
F4	4.6 ± 0.5	0.42	96.8 ± 2.5	28 ± 3
F5	4.6 ± 0.3	0.43	97.9 ± 2.4	22 ± 3
F6	4.3 ± 0.4	0.51	98.1 ± 1.3	20 ± 4
F7	4.2 ± 0.5	0.53	99.2 ± 1.4	17 ± 2
F8	4.2 ± 0.6	0.58	99.5 ± 1.2	17 ± 2

The hardness of all formulation was found good enough to pass the friability criteria. Hence the friability of the formulation is well within the acceptance criteria. The friability was found less than 1 in all formulations. Further,

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the drug content of the formulation batches F1-F8 found within acceptance range. The disintegration time of the F1-F8 batches was found less the 60 seconds. It was found that the amount of SSG is directly affecting to Dt time of formulation.

Drug release study

The drug release data obtained in the *in vitro* drug release for formulations F1-F8 are tabulated in the table no. 6. The plots for cumulative drug release of Zotepine shown in Figure no. 1 All the formulations showed rapid % drug release. But the rapid drug dissolution was noticed in F8 formulations compared to other formulations which release more than 90 % drug in 30 min because of high % of PEG 400 and SSG as compared to other formulation. From the above data it concluded that SSG as disintegrating agent in formulation help to drug release faster than the other agent used in formulation.

Table 6: Drug release study of F1-F8

Formulation	% Drug Release in mins				
	5	10	15	30	60
F1	15.9 ± 2.3	32.8 ± 2.9	46.2 ± 3.4	78.9 ± 3.8	89.5 ± 1.6
F2	19.6 ± 3.1	36.9 ± 3.6	49.2 ± 2.6	81.5 ± 4.2	91.2 ± 1.9
F3	20.5 ± 2.5	39.5 ± 3.4	53.6 ± 3.4	84.2 ± 4.3	92.6 ± 1.5
F4	25.3 ± 1.6	44.3 ± 4.2	59.4 ± 3.3	86.2 ± 2.4	92.3 ± 1.1
F5	29.4 ± 5.4	48.3 ± 1.9	62.5 ± 2.8	88.9 ± 1.6	94.1 ± 1.3
F6	32.8 ± 3.9	49.6 ± 2.9	63.3 ± 2.6	88.9 ± 1.9	94.6 ± 1.2
F7	34.9 ± 3.4	51.8 ± 2.7	65.5 ± 2.7	89.3 ± 2.1	95.1 ± 1.2
F8	**42.1 ± 2.6**	**62.9 ± 3.5**	**75.8 ± 2.3**	**92.6 ± 2.3**	**99.9 ± 0.9**

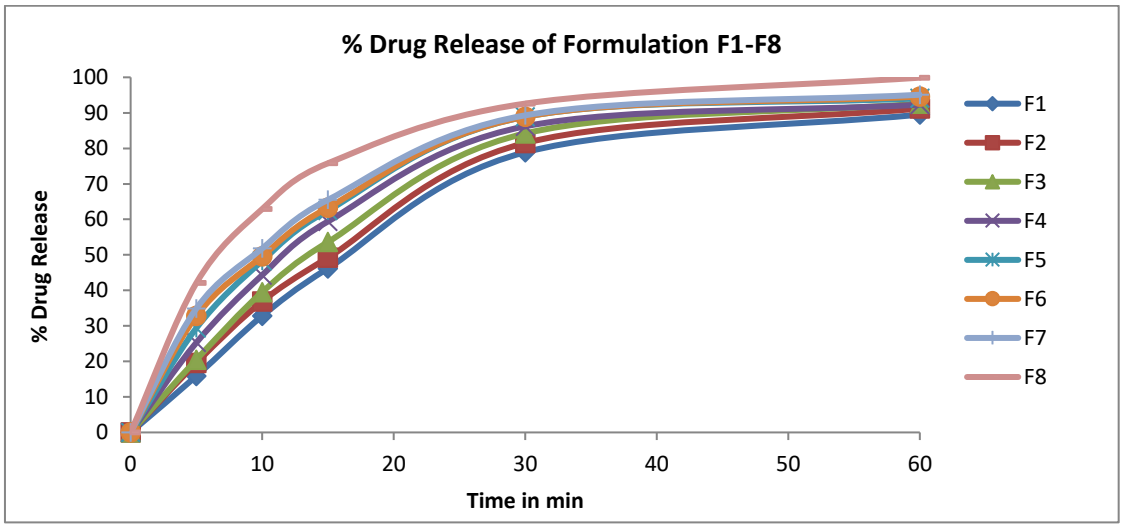

Figure 1. Drug release comparison

Comparison with Marketed Product

Drug release comparison of F8 formulation which is optimized liquisolid compact compared with the marketed product and As such API. The results were shown in below table which clearly indicated that the F8 formulation having a highest drug dissolution rate as compare to marketed product.

Table 7: Comparison with Marketed Product

Batch	% Drug Release in min				
	5	10	15	30	60
API	21.3±0.2	28.8±0.5	31.8±0.9	44.5±0.1	49.4±0.9
Marketed Product	29.6±0.9	37.8±0.2	50.6±0.7	56.9±0.0	60.6±0.4
F8	42.1±2.6	62.9±3.5	75.8±2.3	92.6±2.3	99.9±0.6

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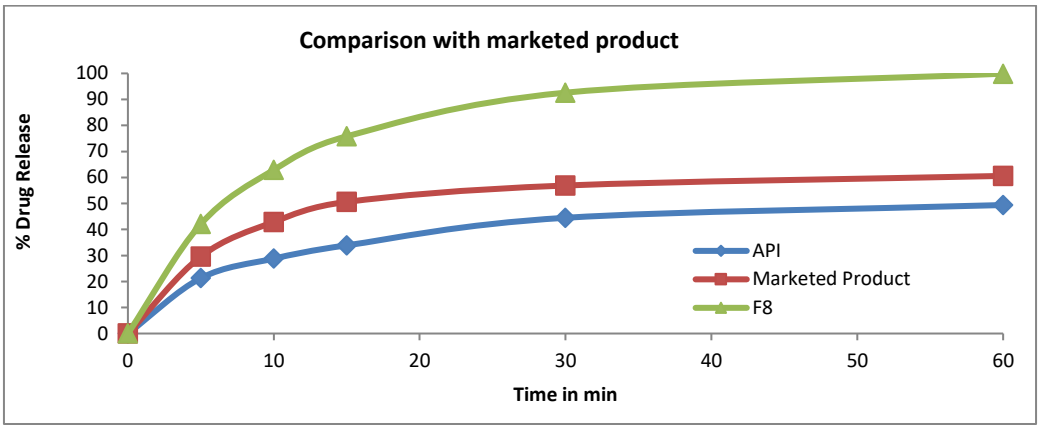

Figure 2: Comparison with marketed product

Stability Study

Stability study of final formulation F8 performed for 1 month and the results were recorded. Formulation found stable during stability study. The stability study was performed in accordance to ICH guideline. The samples were analyzed for various evaluating parameters before and after stability study. The results showed good similarity with that of before evaluated parameters.

CONCLUSION

The liquisolid tablet technique can be effective way for dissolution rate improvement of water insoluble drugs such as Zotepine. Polyethylene glycol (PEG 400) was used as a liquid vehicle. Enhanced dissolution rates obtained in the present study in turn indicates increase in oral bioavailability due to increased wetting and surface area available for dissolution. This novel approach to the formulation may be helpful to improve oral bioavailability.

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