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Research Article

DISSOLUTION RATE ENHANCEMENT OF FEBUXOSTAT BY LIQUISOLID TECHNIQUE

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ABSTRACT

The objective of this present study was to enhance the dissolution rate of poorly soluble drug Febuxostat by delivering the drug as a liquisolid compact. Febuxostat tablet was prepared by Liquisolid compacts technique and it is optimized by using different concentration of drug in non-volatile solvent (PEG400) and different ratio of Carrier (Avicel 102) to adsorbent material (Aerosil 200). The solid state property of liquisolid compact powder was characterized by Fourier Transform Infra-Red Spectroscopy (FT-IR). FTIR studies of Febuxostat and Liquisolid compact powder confirmed that the drug was pure and there is no chemical interaction between drug and excipients. The prepared Liquisolid Tablets were evaluated for hardness, Friability, drug content and *in vitro* dissolution study. The solubility and dissolution rate were found significantly increased in these Liquisolid compact systems compared with pure drug alone. The highest improvement of solubility and dissolution rate was found with 45% w/w Concentration of drug in PEG 400 and 10:1 ratio of carrier to adsorbent material. The dissolution studies for liquisolid compacts and conventional formulations were also been performed and it was found that liquisolid compacts of Febuxostat showed significant higher drug release than conventional. Total of nine formulations were prepared and from that F2 was optimized formulation with drug release of 99.11%.

Keywords: Febuxostat, Liquisolid, PEG 400, Aerosil 200, Avicel 102

INTRODUCTION

The most discussed but still not fully resolved problem, solubility or dissolution augmentation techniques for researchers in formulation science is the most vibrant area. Solubility and dissolution are the basic concepts of any physical or chemical science, including biopharmaceutical and pharmacokinetic considerations in the treatment of any medicine. The solubility of a drug / dissolution behaviour is the key determinant for its oral bioavailability, the latest frequency of rate-limiting measures for the absorption of medicines from gastrointestinal tract. As a result, more than 40% of new candidates entering the drug development pipeline fail due to non-adopting biopharmaceutical properties[1,2].

In these years, various techniques have been employed to increase the dissolution profile and, in turn, the absorption efficiency and bioavailability of water insoluble drugs and/or liquid lipophilic drug[3,4]. Many researchers have shown that Liquisolid Technology is the most promising method to promote dissolution rates of poorly water soluble drugs[5-7]. Liquisolid technology is described by Spiras as fluid might be changed into a free flowing, effectively compressible and dry powder by basic physical mixing with chosen excipients called carrier and coating material (Figure 1). A liquid lipophilic drug can be converted into liquisolid system without being further modified. On the other hand, if a solid water insoluble drug is prepared, then it should be dissolved initially or suspended in appropriate non-volatile solvent system to prepare drug solution or drug suspension of required concentration. Inert, probably water-miscible organic solvent systems with more boiling points and a less viscous organic solvent system such as propylene glycol, liquid polyethylene glycols, poly sorbates, fixed oils, or glycerine are best suitable as liquid vehicles[8,9]. After oral administration to absorb a drug in systemic circulation, the drug should go through dissolution in gastric fluid. The absorption rate of the poorly soluble drug should be formulated in an oral form as a solid dose in order to control its dissolution rate in the liquid present at the absorption site. E.g. the dissolution rate is rate limiting step in drug absorption. Thus oral route is the preferred route of drug administration due to it is convenience, better patient compliance and low production costs. The liquisolid technique is novel concepts, where a liquid will turn into free flowing, readily compressible and apparently dry powders by simple blending with selected carrier and adsorbent material[10,11]. The liquid which can be a liquid drug, a drug suspension or a drug solution in suitable non-volatile liquid vehicles, incorporate into the porous carrier material. Inert, preferable water miscible organic solvent with high boiling point such as liquid polyethylene glycols, propylene glycol or glycerine are most excellent fitting as liquid vehicles[12,13].

Febuxostat is a non-purine-selective inhibitor of xanthine oxidase which is used for treatment of gout. The oral bioavailability of febuxostat is only 49% in healthy humans due to low solubility in water. It works by noncompetitively blocking themolybdenum pterin center which is the active site on xanthine oxidase[14,15].

Hence, the objective of the present study was to formulate the liquisolid compacts for febuxostat to improve the solubility and dissolution rate, which can increase clinical efficacy or may reduce the oral dose required to achieve the same effect.

MATERIAL AND METHODS

Febuxostat was obtained as a gift sample from Zydus Cadila healthcare Ltd. Ahmadabad. Polyethylene glycol 400, Avicel PH 102, Aerosil 200, Magnesium Stearate obtained from Chemdyes Corporation, Vadodara. Disintegrating agent Crospovidone obtained from Arihant trading co, Mumbai.

Methods

Solubility Studies

The solubility of Febuxostat were carried out in different non-volatile liquid like Propylene glycol, PEG-200, PEG-400, PEG-600, Tween 20, Span 80 etc. were performed for the development of liquisolid tablets. Saturated solutions were prepared by adding excess amount of Febuxostat to the vehicles and stirred on stirrer for 24 hours at 25°C under constant stirring speed. After this period the solutions were filtered through a whatman filter paper, diluted with methanol and analyzed by UV-spectrophotometer at a wavelength of 314 nm. From these results, the solubility of Febuxostat in the respective liquid vehicle was calculated.[16]

Pre formulation Studies

Flow properties were determined on prepared liquisolid powder before compression of tablets. In which the carr's index, hausner's ratio and angle of repose was measured.[17]

Preparation of Liquisolid Compacts

The liquisolid tablet preparation method involve, First a mathematical calculated amount of pure drug weigh and dissolve in the suitable amount of non-volatile in molecularly dispersed state. This liquid medication was poured into the suitable amount of carrier material. The liquid medication absorbed into carrier material internally and externally. Adsorbent material was added for dry looking, non-adherent for achieving good flow and compressible properties. Both absorption and adsorption take place step by stepwise. The liquid medication absorbed into porous carrier particles till saturation achieved and adsorption of adsorbent on to the external surface of porous particle. Disintegrant and other excipient like binder and lubricants were added to prepare final blend. The final mixture was compressed into tablets using rotary punching machine. Formulation parameters are summarized in Table 1.[18,19]

Pre Compression Studies of Prepared Liquisolid Compacts

The powder blends of various formulations were assessed for angle of repose, mass density (obvious and tapped) and compressibility index. The fixed funnel strategy was utilized to measure the angle of repose (θ) and it was determined utilizing the accompanying formula:

$$\text{Tan } \theta = h/r$$

In which, θ is angle of repose, h is height of the cone and r is radius of the cone's bottom part. Angle of repose under 300 demonstrates the free flowing of the material.

The tapping strategy was utilized to decide the tapped density, bulk density and percent compressibility index. The compressibility index (Carr's Index) is a proportion of the affinity of a powder to be compacted. It is resolved from the bulk and tapped densities and is calculated using the following formula:

$$\text{Carr's Index} = [(\rho_{tap} - \rho_b) / \rho_{tap}] / \times 100$$

In which, ρ_b is bulk density and ρ_{tap} is tapped density.[20]

Drug-Polymer Interaction Studies

To investigate the possible physical and chemical interactions between the drug and excipients was determined by using FTIR spectroscopy. The FTIR spectra of drug, Avicel PH102, Aerosil 200 and mixture were recorded on perkin elmer spectrophotometer (perkin elmer Inc., MA, Us) using KBr pellet from 4000 cm^{-1} to 400 cm^{-1} range.[20]

Post Compression Characterization

The prepared tablets were characterized for different parameters such as hardness, friability, diameter, thickness, weight variation. The hardness of ten tablets was measured using Monsanto Hardness Tester. Mean and standard deviation were computed and reported. It was expressed in kg/cm^2. The friability of tablets was determined by Roche Friabilator (electro lab, Mumbai, India) and the percentage weight loss during the friability was not exceeded by 1% of the initial weight. For estimating weight variation 20 tablets as per USP were randomly selected from each batch and weighed individually. The average weight and standard deviation of 20 tablets was calculated. The disintegration test was performed using Electro lab disintegrating apparatus to determine disintegration time. One tablet was placed in each of the six tubes of the basket and the apparatus was operated using distilled water maintained at 37 ± 0.5^0 C as the immersion fluid. The time required for complete disintegration of tablet was noted.[20]

Determination of Drug Content

For estimation of drug content, one tablet was finely powdered and transferred to a 100 ml volumetric flask, then 70 ml of buffer (0.1 N HCl) was added. The flask was shaken for 10 min. Finally, the volume was made up to the mark with the same buffer solution. The resultant solution was then filtered and 1 ml of the filtrate was suitably diluted up to 100 ml with same buffer solution and analyzed for febuxostat content at 314 nm using a double beam UV/Visible spectrophotometer (Shimadzu 1800, Japan) and 0.1N HCL as blank.[21,22]

In-Vitro Dissolution Study of Formulation

In- vitro drug release study was performed using USP apparatus II in a dissolution media of 0.1 N HCL for 1 h. The volume of dissolution media was 900 ml. The dissolution was performed at 37 ± 0.5° C temperature and an RPM of 50. The samples were collected at different time intervals for 1 h by glass pipette and evaluated by U.V visible spectroscopy method.[22]

Stability Study

The accelerated stability studies were carried out on the optimized formulation F2. The formulations were stored at 40 ± 2°C/75 ± 5% RH for 90 days to assess their long term stability. The results indicated that, irrespective of the concentration of polymer, these formulations remained stable for 30 days. By comparison it was found that febuxostat *in vitro* release was found to be 99.11 % at zero day, 99.10 % at 15 days and 99.05 % at 30 days. It was found that a period of 30 days storage there were no changes in the physical as well as drug release pattern.[23]

Table 1: Formulation of Febuxostat Liquisolid Tablets

Batch No.	Drug conc. in PEG 400 (%w/w)	Drug (mg)	PEG 400 (mg)	Q:q (R)	Lf	Q (mg)	q (mg)	CP 5 % (mg)	Mg. Stearate 1% (mg)	Total (mg)
F1	40%	40	100	10:01	0.483	289.85	28.98	24.34	4.88	488.06
F2	45%	40	88.88	10:01	0.483	266.83	26.68	22.45	4.49	449.33
F3	50%	40	80	10:01	0.483	248.44	24.84	20.89	4.18	418.36
F4	40%	40	100	15:01	0.387	361.75	24.11	27.94	5.59	559.4
F5	45%	40	88.88	15:01	0.387	333.02	22.2	25.73	5.14	514.97
F6	50%	40	80	15:01	0.387	310.07	20.67	23.95	4.79	479.48
F7	40%	40	100	20:01	0.34	411.76	20.58	30.56	6.08	608.99
F8	45%	40	88.88	20:01	0.34	379.05	18.95	27.85	5.6	560.34
F9	50%	40	80	20:01	0.34	352.94	17.64	26.07	5.21	521.86

Table 2: Flow ability Parameters of Febuxostat Liquisolid Powder Systems

Batch No.	Bulk Density (gm/cc)	Tap Density (gm/cc)	Carr's Index (%)	Hausner's Ratio	Angle of repose (Ɵ)
F1	0.372 ± 0.002	0.445 ± 0.003	16.08 ± 0.33	1.174 ± 0.012	32.96 ± 0.24
F2	0.364 ± 0.003	0.434 ± 0.002	14.95 ± 0.20	1.191 ± 0.016	31.87 ± 0.27
F3	0.371 ± 0.002	0.461 ± 0.001	19.14 ± 0.14	1.236 ± 0.016	32.49 ± 0.27
F4	0.376 ± 0.002	0.455 ± 0.002	17.39 ± 0.30	1.210 ± 0.012	34.11 ± 0.80
F5	0.369 ± 0.002	0.447 ± 0.001	17.39 ± 0.28	1.210 ± 0.012	33.13 ± 0.49
F6	0.362 ± 0.003	0.442 ± 0.002	18.04 ± 0.23	1.220 ± 0.014	33.77 ± 0.68
F7	0.376 ± 0.001	0.467 ± 0.001	19.81 ± 0.18	1.247 ± 0.018	36.07 ± 0.17
F8	0.375 ± 0.002	0.465 ± 0.002	19.34 ± 0.16	1.239 ± 0.010	35.67 ± 0.69
F9	0.367 ± 0.002	0.457 ± 0.003	19.39 ± 0.22	1.240 ± 0.012	33.98 ± 0.46

Where n = 3, Mean ± SD

Table 3: Weight Uniformity, Hardness, Friability, Disintegration Time and Drug Content

Batch No	Weight Uniformity (mg)	Hardness (kg/cm^2)	Friability (%)	Tablet Disintegration time (sec.)	Drug Content (%)
F1	488.4 ± 5.02	4.21 ± 0.05	0.533 ± 0.025	356 ± 4.89	95.89 ± 0.71
F2	450.4 ± 3.85	3.76 ± 0.10	0.599 ± 0.012	235 ± 3.89	97.11 ± 1.25
F3	419.8 ± 4.29	3.96 ± 0.05	0.581 ± 0.021	261 ± 3.14	95.31 ± 1.58
F4	558.9 ± 5.37	5.16 ± 0.20	0.308 ± 0.011	438 ± 3.14	94.86 ± 1.80
F5	512.7 ± 5.21	4.73 ± 0.20	0.379 ± 0.020	405 ± 2.89	95.57 ± 1.34
F6	478.7 ± 4.45	3.83 ± 0.05	0.542 ± 0.016	271 ± 3.09	96.35 ± 1.56
F7	606.1 ± 5.31	5.73 ± 0.30	0.290 ± 0.022	469 ± 3.83	96.36 ± 1.25
F8	561.4 ± 4.75	5.06 ± 0.20	0.333 ± 0.010	383 ± 2.09	96.25 ± 0.71
F9	521.8 ± 4.48	4.06 ± 0.10	0.360 ± 0.015	327 ± 3.38	95.11 ± 0.71

Where n = 3, Mean ± SD

In-Vitro Drug Release Study

Table 4: Dissolution Profile Comparison of Batch F2-Medicated Powder with Pure Drug

Time (minutes)	F2 medicated powder (%)	Pure drug (%)
0	0	0
10	12.55 ± 1.15	2.57 ± 1.12
20	21.55 ± 1.33	3.66 ± 1.21
30	38.15 ± 1.23	6.37 ± 1.17
40	53.40 ± 1.17	11.45 ± 1.20
50	68.65 ± 1.08	17.61 ± 1.12
60	81.99 ± 1.20	25.47 ± 1.15

Where n = 3, Mean ± SD

Table 5: Dissolution Profile Comparison of Batch F2 with Marketed Tablet-LO-URIC® (40.0 Mg)

Time (minutes)	F2 (%)	LO-URIC (%)
0	0	0
10	13.09 ± 1.25	6.57 ± 1.25
20	22.45 ± 1.29	10.66 ± 1.17
30	39.06 ± 1.23	19.37 ± 1.20
40	55.40 ± 1.20	29.45 ± 1.12
50	68.72 ± 1.06	40.61 ± 1.07
60	82.21 ± 1.10	54.49 ± 1.22

Where n = 3, Mean ± SD

Table 6: Stability Study Data of Optimized Batch F2

S. No.	Parameters	Storage Periods (Days) at 40 ± 2 °C Temperature and 75 ± 5 % Relative Humidity		
		Before Storage	**After 15 days**	**After 30 days**
1	Spot formation Stickiness	Negative	Negative	Negative
2	Hardness	3.7 ± 0.10	3.7 ± 0.10	3.6 ± 0.10
3	Friability	0.399 ± 0.012	0.395 ± 0.014	0.396 ± 0.012
4	Drug content	99.11 ± 1.45	99.10 ± 1.53	99.05 ± 1.65
5	*In-vitro* drug release (%) at 30 min	38.15 ± 1.06	37.56 ± 1.12	37.63 ± 1.10

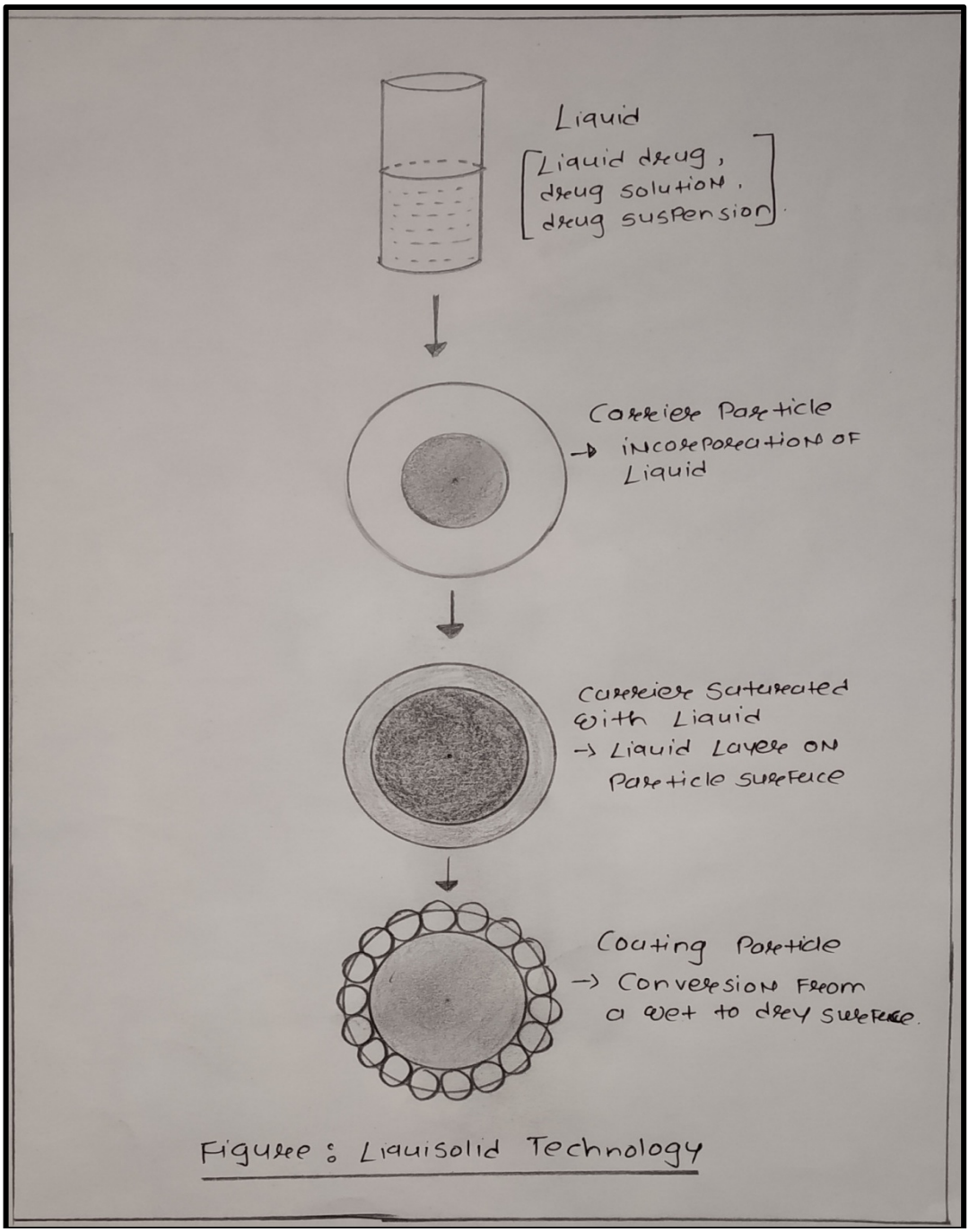

Figure 1: Liquisolid Technology

RESULT AND DISCUSSION

The flow ability parameters of all 9 batches are shown in Table 2 which indicates that bulk density are in range of 0.372 ± 0.002 to 0.362 ± 0.003 g/cc, tap density are in range of 0.467 ± 0.001 to 0.434 ± 0.002 g/cc, Carr's index falls in the range of 19.81 ± 0.81 to 14.95 ± 0.20%, Hausner's ratio falls in the range of 1.247 ± 0.018 to 1.174 ± 0.012 this is also supported by angle of repose which is in range of 36.07 ± 0.17 to 31.87 ± 0.27. This indicates that the prepared powder blend for tablet is having good compressible characteristics so direct compression method was suitable for the preparation of tablets; which is also cheap in cost and time saving method for the tablet preparation.

Table 3 shows the weight variation which was found in range of 606.1 ± 5.31 to 419.8 ± 4.29 mg, hardness and friability of all formulations was found within acceptable limits. Hardness of prepared tablets was found in range of 5.73 ± 0.30 to 3.76 ± 0.10 kg/cm^2, friability of all tablets was found in range of 0.599 ± 0.012 to 0.290 ± 0.022 %. So, from the results of hardness it was concluded that tablet will not get breakdown easily upon handling and storage. While from the results of friability it was concluded that loss in content and weight of tablet is negligible. Tablet disintegration time of all batches was found in range of 235 ± 3.89 to 469 ± 3.83 seconds, the drug content of the prepared tablets was in the range of 97.11 ± 1.25 to 94.86 ± 1.80 %. This indicates that the prepared tablets are of good quality.

Table 4 shows dissolution profile comparison of batch F2 medicated powder with pure drug. In which dissolution profile of F2 medicated powder was in range of 12.55 ± 1.15 to 81.99 ± 1.20 % while dissolution profile of pure drug was in range of 2.57 ± 1.12 to 25.47 ± 1.15 % for the time period of 0 to 60 minutes. This indicates that the prepared medicated powder by using liquisolid technique has higher solubility than pure drug.

Table 5 shows dissolution profile comparison of batch F2 tablet with marketed tablet. In which dissolution profile of F2 tablet was in range of 13.09 ± 1.25 to 82.21 ± 1.10 % while dissolution profile of marketed tablet was in range of 6.57 ± 1.25 to 54.49 ± 1.22 % for the time period of 0 to 60 minutes; so from this comparison it's been concluded that F2 batch is having better dissolution profile than marketed formulation.

Table 6 shows the stability study of optimized batch F2 in which it was found that there was not significant change in appearance, hardness, friability, drug content and *in vitro* drug release profile behaviour. So it's been concluded that the prepared formulation was stable after 1 month.

CONCLUSION

The present study concludes that the liquisolid compaction was found to be a promising technique for improving the dissolution of poorly soluble drug like Febuxostat and the dissolution profile of optimized batch F2 was found to be better than marketed formulation. The stability studies showed that the drug content, hardness, friability and dissolution of liquisolid formulation were not affected by ageing significantly.

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