Original Article

Formulation and Evaluation of Carbamazepine Liquisolid Compacts Using Novel Carriers

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ABSTRACT

Objective: The aim of present investigation was to prepare liquisolid compacts of high dose water insoluble drug, carbamazepine (CBZ) using novel porous carriers such as Neusilin and Fujicalin in order to improve its dissolution rate and reduce the tablet weight. **Materials and Methods:** Solubility of CBZ was determined in different non volatile solvents to finalise vehicle having maximum solubility. The liquid retention potential (ϕ) of carriers and coating material was determined and 18 different liquisolid compacts of CBZ were formulated. The prepared liquisolid compacts were evaluated and compared for thickness, diameter, weight variation, uniformity of content, hardness, friability, disintegration and *in vitro* dissolution. Dissolution profile of liquisolid compacts was compared with marketed tablet formulation. **Results and Discussion:** The solubility of CBZ in polyethylene glycol 200 was found to be greater than the other solvents. Neusilin showed higher ϕ value than traditional carriers. Formulated liquisolid compacts showed all physical parameters within prescribed limit. Formulation containing Neusilin-Neusilin and Neusilin-Aerosil showed no disintegration while all other formulations showed disintegration up to 180 seconds. All the formulations showed drug release above 80% at the end of 15 minutes except marketed formulation. The weight of formulations containing Neusilin and Fujicalin ranged in between 0.383-0.947g. Formulation FA3 containing Fujicalin exhibited lower mean dissolution time and higher dissolution efficiency than all other formulations including marketed tablet. **Conclusion:** It can be concluded from this study that novel porous carriers are superior to traditional carriers in liquisolid systems and are suitable for loading high dose drugs like CBZ.

Key words: Avicel, Carbamazepine, Dissolution enhancement, Fujicalin, Liquisolid compact, Neusilin.

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INTRODUCTION

The oral solid dosage form must ensure dissolution in order to absorb from the gastrointestinal tract. The poor dissolution rates and inadequate absorption characteristics of water-insoluble drugs are major problems faced by the pharmaceutical industry.[1] Various techniques have been employed to enhance the dissolution profile of water insoluble drugs such as amorphisation of drug,[2] particle size reduction by micronisation,[3] cogrinding,[4] inclusion complexation,[5,6] solid dispersion,[7] self emulsifying drug delivery system,[8] nanosuspension,[9] hot melt extrusion[10] and adsorption of drugs to hydrophilic silica aerogels.[11] Recently, liquisolid compacts has emerged as a promising technique for improving the dissolution rate of poorly soluble drugs.[12] The concept of "liquisolid systems" as defined by Spireas *et al*. (1999) may be used to convert a liquid into a free flowing, readily compressible, and apparently dry powder by simple physical blending with selected excipients named the carrier and coating material.[13] The liquisolid compact significantly increases wetting properties and surface area of drug available for dissolution. The liquisolid compacts of water-insoluble substances

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may be expected to show enhanced drug dissolution which results in improved bioavailability.[14]

The technique of liquisolid compact has been successfully employed to improve the *in vitro* release of poorly soluble drugs like indomethacin,[15] piroxicam,[16] griseofulvin,[17] ezetimibe,[18] repaglinide,[19] prednisolone,[1] etc. The liquisolid technology for release enhancement has been successfully applied to low dose poorly soluble drugs. But, the formulation of a high dose poorly soluble drug is one of the limitations of this technology.[20] In order to increase drug loading, the powder must retain high amount of liquid. However, this may lead to poor flow and compression properties of the powder. In order to maintain good flow and compression properties, high amount of carrier and coating material should be used. But, this may result in an increase in tablet weight ultimately leading to an unacceptably large tablet size. The tablet size is a key determinant in the patient compliance.

Therefore, a potential approach to load high dose of water insoluble drug is to increase the liquid adsorption capacity by using carrier and coating materials such as Neusilin and Fujicalin with a high specific surface area (SSA) which maintains flow of material, compression properties and reduces tablet weight.[17] Fujicalin is a spherically granulated anhydrous dicalcium phosphate while Neusilin US2 is a synthetic amorphous form of magnesium aluminometa silicate.[21]

Carbamazepine (CBZ) is routinely used in the treatment of epilepsy and trigeminal neuralgia for over 40 years.[22] The dose of CBZ is 100-200 mg once or twice daily. Its oral bioavailability is 72-96%.[23] It is practically insoluble in water. The oral absorption of CBZ is slow, erratic and unpredictable in humans owing to slow dissolution.[24] Hence, it is necessary to improve dissolution rate which in turn may improve the bioavailability of drug. The various techniques such as solid dispersion,[25] complexation,[26] cocrystals,[27] and liquisolid compact[28] were reported previously in order to enhance the dissolution rate of CBZ. Also, Javadzadeh *et al*. (2007), have formulated liquisolid compacts of CBZ using PVP and concluded that high amounts of drug can be loaded into liquisolid compacts by adding PVP to liquid medication.[29]

In view of above facts, we thought to evaluate and compare novel porous carriers such as Neusilin and Fujicalin for increasing loading capacity of non volatile solvent along with the drug, so that liquisolid compact of high dose poorly water insoluble model drug CBZ can be formulated. The prepared formulations were characterized and compared with marketed formulation (Tegretol) of CBZ.

MATERIALS AND METHODS

Materials

CBZ was received as gift sample from Abbott Healthcare Pvt. Ltd, Mumbai. Neusilin US2 and Fujicalin SG were obtained as gift sample from Gangwal Chemicals Pvt. Ltd, Mumbai. Aerosil 200, Crospovidone (Polyplasdone XL 10) and Avicel PH102 were obtained as gift sample from Centaur Pharmaceuticals Pvt. Ltd., Pune. Polyethylene glycol (PEG) 200 purchased from Loba Chemie, Mumbai. All other excipients and reagents used were of pharmaceutical grade and used as received.

Solubility studies

The saturation solubility studies were carried out in four different non volatile solvents i.e. propylene glycol (PG), PEG 200, PEG 400, Tween 20 so as to select the best non volatile solvent for preparation of liquid medication. In brief, excess amount of CBZ was mixed with four non-volatile solvents separately in 50ml vials. The mixtures were shaken on shaker (Bio-Technics, India) for 48 hours. Then solutions were filtered through 0.45µ membrane filter and diluted suitably with 1% sodium lauryl sulphate (SLS) and analyzed UV spectrophotometrically (UV 1700, Shimadzu, Japan) at 287 nm for their drug content. Three determinations were carried out for each sample to calculate the solubility of CBZ.[6]

Determination of Angle of Slide

The "Angle of slide" measurement was used to evaluate the flow property of powder excipients (Avicel PH102, Aerosil 200, Neusilin US2, Fujicalin SG) with liquid vehicles. Several uniform liquid vehicle/powder admixtures which contain 10 g of the carrier or coating materials with increasing amounts of liquid vehicle (PEG 200) were prepared.

To measure the angle of slide, the prepared powder admixtures were placed on polished metal plates, the plates were tilted gradually until the powder admixture was about to slide. The angle formed between the plate and the horizontal surface was expressed as the angle of slide (ø). The angle of slide corresponding to 33^0 corresponded to optimal flow properties.[30]

Determination of flowable liquid retentions potential (ф) of carrier and coating material

The flow properties of excipients will be changed due to adsorption of the liquid vehicle. The flowable liquid-retention potential (ф-value) of each liquid/powder admixture was calculated using the following equation.

Φ value = weight of liquid/weight of solid

The ф -values were plotted against the corresponding angle of slide (ø). An angle of slide (for optimal flow properties) corresponding to 33° of a liquid/powder admixture represented the flowable liquid-retention potential, ф -value, of its powder which is required for preparation of liquisolid tablets. All measurements were carried out in triplicate.[30]

Preparation of liquisolid system

The amount of excipients used to prepare liquisolid compact depends on their ф-values as well as liquid load factors. In current studies, Avicel 102, Neusilin US2 and Fujicalin SG were used as carrier while Aerosil 200 and Neusilin US2 were used as coating material.

The liquid load factor (L_f) is calculated by using following formula

$$L_f = ф + ø\ (1/R) \quad (1)$$

$$L_f = W/Q \quad (2)$$

$$R=Q/q \quad (3)$$

Where, ф and ø are the values of the carrier and the coating powders respectively while R is excipient ratio. The CBZ was suspended in PEG 200 in the concentration (% C_d) of 50, 70 and 90 %. The total 18 batches were formulated as given in Table 1.

Preparation of CBZ tablets

The liquisolid powder mixture containing CBZ was compressed directly by using single punch tablet machine to get tablets of 10, 12 and 14mm diameter with desired thickness and hardness.

EVALUATION OF LIQUISOLID TABLETS

Physical parameters of tablets

Tablets were evaluated by carrying out tests for weight variation, uniformity of tablet thickness and diameter, friability and hardness (EH-01, Electrolab, Mumbai). All the tests were carried out in triplicate as per the compendial specifications.[31,32]

Content uniformity

The drug content uniformity was determined as per IP 1996. The 20 tablets were weighed and powdered. The quantity of powder equivalent to 100 mg of drug was weighed and transferred to 100 ml volumetric flask containing 60 ml of ethanol (95%). The flask was shaken to dissolve the drug and volume was adjusted with ethanol. 10 ml of this solution was filtered and diluted to 100 ml with ethanol and absorbance of resulting solution was

Table 1: Formulation of liquisolid compact of CBZ

Carrier & Coating Material	Batch code	% Cd	Lf	R	W	Q	q	Crosspovidone 5 %	DCP 10%	Total Wt
Carrier	AA1	90	0.215	20	0.125	0.58	0.029	0.042	-	0.889
Avicel102	AA2	70	0.24	15	0.16	0.66	0.044	0.049	-	1.032
Coating- Aerosil 200	AA3	50	0.44	5	0.224	0.50	0.102	0.047	-	0.994
Carrier - Fujicalin SG Coating – Aerosil 200	FA1	90	0.41	20	0.125	0.30	0.015	0.027	-	0.580
Carrier - Neusilin	FA2	70	0.41	20	0.16	0.38	0.019	0.034	-	0.710
Coating – Aerosil	FA3	50	0.41	20	0.224	0.53	0.026	0.045	-	0.947
200	NA1	90	1.02	20	0.125	0.12	0.006	0.018	-	0.383
	NA2	70	1.02	20	0.16	0.15	0.007	0.021	-	0.457
	NA3	50	1.02	20	0.224	0.21	0.01	0.028	-	0.593
Carrier - Neusilin	NAD1	90	1.02	20	0.125	0.121	0.006	0.018	0.036	0.419
Coating – Aerosil	NAD2	70	1.02	20	0.16	0.156	0.007	0.021	0.043	0.501
200	NAD3	50	1.02	20	0.224	0.218	0.010	0.028	0.056	0.650
Carrier - Neusilin	NN1	90	0.99	20	0.125	0.125	0.006	0.018	-	0.387
Coating -Neusilin	NN2	70	0.99	20	0.16	0.16	0.008	0.022	-	0.462
	NN3	50	0.99	20	0.224	0.224	0.011	0.028	-	0.600
Carrier - Neusilin	NND1	90	0.99	20	0.125	0.125	0.006	0.018	0.036	0.423
Coating -Neusilin	NND2	70	0.99	20	0.16	0.16	0.008	0.022	0.044	0.506
	NND3	50	0.99	20	0.224	0.224	0.011	0.028	0.057	0.657

% Cd= Concentration of drug in non volatile solvent, Lf=liquid load factor, R= Excipient ratio, W= weight of non-volatile solvent, Q= Carrier, q= coating material; DCP-dicalcium phosphate

measured spectrophotometrically at maximum wavelength of 285nm.[33]

Disintegration test

For most of the tablets, the foremost important step towards solution is breakdown of tablet into smaller particles or granules, a process known as disintegration. The disintegration test was carried out as described under procedure for uncoated tablets in IP 1996. The assembly was suspended in the liquid medium (water) in the suitable vessel, preferably in 1000 ml beaker (ED-2L, Electrolab, Mumbai). The volume of the liquid such that the wire mesh at its highest point is at least 25 mm below the surface of liquid and its lower point is at least 25 mm above the bottom of the beaker. A thermostatic arrangement was made for heating the liquid and maintaining the temperature at 37 ± 2°C. Assembly was suspended in beaker containing 1000 ml of distilled water and the apparatus was operated for specified time. Also disintegration time of tablet was recorded. Finally the assembly was removed from liquid.[33]

Dissolution studies

The dissolution test was used to compare the release of CBZ from liquisolid tablets and marketed tablet, Tegretol. The USP Apparatus 2 (Electrolab, TDT-06L) was used with 900 ml of 1% sodium lauryl sulphate solution (1% SLS) at 37 ± 0.5 ^{0}C, and rotated at 75 rpm. One millilitre sample was withdrawn after specified time intervals and sink condition was maintained. The samples were filtered, diluted suitably and analysed spectrophotometrically at 287 nm wavelength.[28]

Dissolution profiles of formulations were compared on the basis of dissolution efficiency (DE) and mean dissolution time (MDT) with marketed formulation.[34]

IR- spectroscopy

IR spectrum of CBZ, Avicel102, Aerosil200, PEG200, NeusilinUS2, Fujicalin SG and optimized formulations AA2, FA3, NAD2, and NND3 were recorded on ATR Fourier Transform Infrared Spectrophotometer (IRAffinity, MIRacle 10, Shimadzu, Japan). Small quantity of sample was taken and directly put on ATR diamond. The sample was pressurized with the help of pressure arm. Then the spectrum was scanned in the wavelength region of 4000 to 400 cm^{-1}.

X-ray powder diffraction

X-Ray powder diffraction (XRD) analysis was performed in order to study the change in the crystallinity of CBZ within the liquisolid complex. XRD of CBZ, formulation AA2, FA3, NAD2 and NND3 were recorded using Bruker D2 Phaser diffractometer using Cu Kα1 radiation with l = 1.5418 Å.

Differential Scanning calorimetry

Differential scanning calorimetry (DSC) analysis was conducted to study the interaction in between CBZ and other components of liquisolid compacts. DSC was carried out on the CBZ and optimized formulations AA2, FA3, NAD2, NND3 using Model-SDT Q600 V20.9 Build 20 with a computerized data station. Samples were placed in an aluminium pan and heated at a rate of 10°C/min in the temperature range of 30–300°C. The thermal analysis was performed under nitrogen atmosphere.

Statistical analysis

The results were expressed as mean±SD. Statistical analysis was carried out by one way analysis of variance (ANOVA) using GraphPad Prism. $p<0.05$ was considered as the minimal level of statistical significance.

RESULTS AND DISCUSSION

Solubility studies

Solubility of CBZ in propylene glycol, PEG 200, PEG 400, glycerine and Tween 20 is given in Table 2. CBZ showed maximum solubility in PEG 200 (107.94 mg/ml) and lowest in Tween 20 (6.84 mg/ml). This is due to dispersion of higher fraction of drug in PEG 200 which helps to improve dissolution of drug.

Table 2: Solubility data of CBZ

Non volatile solvent	Solubility (mg/ml)
Propylene Glycol	45.10±0.16
PEG 400	68.12±0.29
PEG 200	107.94±0.62
Tween 20	6.84±0.11

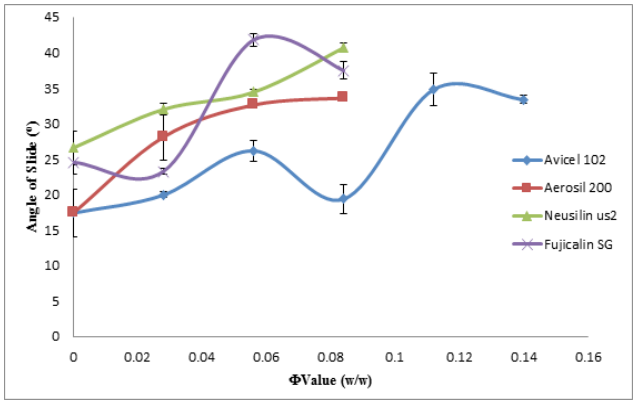

Figure 1: Relation between ϕ values and Angle of slide

Table 3: Physical parameters of CBZ tablets					
Formulation Code	Thickness* (mm)	Diameter* (mm)	Hardness* (kg)	Friability (%)	Weight Variation* (mg)
AA1	4.62±0.044	14.05±0.074	5.28±0.13	0.26	888.6±3.69
AA2	5.5±0.122	14.04±0.045	6.75±0.11	0.19	1031±2.88
AA3	5.12±0.044	14.03±0.065	4.79±0.22	0.25	993±2.53
FA1	4.84±0.054	10.16±0.054	3.18±0.078	0.98	565±7.22
FA2	4.06±0.054	12.22±0.044	3.27±0.079	0.96	688±1.56
FA3	4.06±0.11	14.2±0.070	3.9±0.0164	0.85	920±1.73
NA1	4.14±0.054	10.2±0.070	4.59±0.08	0.54	383±2.88
NA2	4.84±0.054	10.22±0.044	4.9±0.78	0.44	458±2.55
NA3	4.78±0.11	12.12±0.045	4.96±0.11	0.21	593±5.11
NAD1	4.84±0.054	10.22±0.044	3.48±0.062	0.71	422±1.53
NAD2	5.28±0.044	10.3±0	3.57±0.008	0.69	504±2.98
NAD3	4.58±0.044	12.3±0.0	3.66±0.031	0.56	655±2.01
NN1	3.86±0.54	10.24±0.054	4.15±0.131	0.23	388±2.4
NN2	4.66±0.089	10.26±0.054	4.35±0.13	0.21	463±3.7
NN3	4.18±0.083	12.26±0.54	4.23±0.081	0.18	599±1.22
NND1	4.34±0.054	10.3±0	3.22±0.062	0.56	414±1.63
NND2	5.24±0.054	10.3±0	3.71±0.023	0.52	492±7.06
NND3	4.54±0.054	12.26±0.054	3.40±0.04	0.48	641±2.27

*All values are expressed as mean ± SD (n=3)

Determination of flowable liquid retentions potential (ϕ) of carrier and coating material

Relation between angle of slide of carrier and coating material in PEG 200 and corresponding ϕ values is given in Figure 1. Neusilin and Fujicalin showed greater ϕ values i.e 0.95 and 0.35 respectively than Avicel 102 (0.14) due to high specific surface area. Neusilin and Fujicalin can load maximum amount of liquid and maintain good flow properties. Though, Aerosil 200 exhibited highest ϕ value (1.5), it was used as coating material.

Evaluation of liquisolid tablet

Physical parameters of tablets

All the physical parameters of liquisolid tablets are shown in Table 3. Thickness of liquisolid compacts were ranged from 3.86 ± 0.54 to 5.5 ±0.122 mm and diameter of all the liquisolid compacts was found to be in the range of 10.16 to 14.5 mm. Liquisolid compact formulated with Neusilin and Fujicalin as carrier showed less diameter and thickness as compared to the Avicel 102. This is due to high SSA of carrier which enabled to load higher amount of liquid. Hardness of tablets was found to be in the range of 3.15±0.131 kg to 6.75±0.11. It was observed that liquisolid compact formulated by using Avicel 102 as carrier showed greater compactibility as compared to other carriers. This may be due to hydrogen bonding between adjacent cellulose

Table 4: Evaluation of CBZ liquisolid formulations		
Formulation code	Disintegration Time* (sec.)	% Drug Content
AA1	103.6±2.50	95.51
AA2	105.4±1.81	97.3
AA3	228.2±4.61	98.5
FA1	19±1.26	96.58
FA2	22.83±1.16	104.1
FA3	27±2.09	102.1
NA1	No disintegration	98.68
NA2	No disintegration	95.98
NA3	No disintegration	98.65
NAD1	178.4±1.51	101.2
NAD2	176±0.70	103.6
NAD3	174.4±1.14	98.5
NN1	No disintegration	99.5
NN2	No disintegration	96.35
NN3	No disintegration	101.2
NND1	180±1.70	98.32
NND2	175.8±0.83	96.54
NND3	173±0.70	98.2

*All values are expressed as mean ± SD (n=3)

molecules in Avicel 102 which causes deformation of the particles plastically leading to formation of strong compact.[35] Liquisolid compact containing Neusilin showed good compactibility, due to its high specific surface area and porosity.[36]

Disintegration time

Disintegration time of liquisolid compact tablets is given in Table 4 and complies as per IP specifications for all formulated batches except formulations containing Neusilin-Aerosil and Neusilin-Neusilin as these batches failed to disintegrate. Therefore, additional 10% DCP was added to these compacts, which may act as pore forming agent helping to disintegrate tablets. Fujicalin compacts disintegrate much faster than Avicel compacts. This may be due to less hardness of Fujicalin compacts as compared to Avicel compacts. Poor disintegration time of Neusilin compact is due to poor disintegration properties of the silicate.[17] However, the improvement in disintegration of these compacts was found after addition of 10% DCP.

Content uniformity

A fundamental quality attribute for all pharmaceutical preparations is the requirement for a constant dose of drug between individual tablets. Uniform drug content was observed for all the formulations which is as per the IP specification (Table 4).[33]

Dissolution Studies

Figure 2 illustrates the *in vitro* drug release profile of the liquisolid formulations. It was found that the drug release rate from the formulations was affected by disintegration time, concentration of drug in PEG 200 and the properties of the carrier and coating material. The formulations which exhibited minimum disintegration time and low drug concentration in PEG 200 showed rapid drug release. A decrease in concentration of drug in PEG 200 increases the dispersion of drug at molecular level which may further enhance the dissolution rate of the drug.

In order to understand effect of carriers on drug dissolution various batches with same excipient ratio and concentration of drug in non volatile solvent were compared. The rate and extent of drug release from batches AA1, FA1, NAD1 and NND1 was found to be different. Batches formulated with Avicel and Fujicalin showed initial faster release upto 30 min than the batches with Neusilin. This may be due to differences in tablet hardness as well as disintegration and physicochemical properties of carriers.

The enhanced dissolution rates of liquisolid compacts compared to marketed tablet may be attributed to the fact that, the drug is already in PEG 200 while at the same time, it is carried by the powder particles. Thus, its release is accelerated due to its increased wettability and surface availability to the dissolution medium. The wettability of the compacts by the dissolution media is one of the proposed mechanisms for explaining the enhanced dissolution rate from the liquisolid compacts.[12] PEG facilitates wetting of drug particles by decreasing interfacial tension between dissolution medium and tablet surface.

It was observed that FA2, FA3, NAD2, NAD3, NND2 and NND3 showed more than 95% of drug release in 30 min. Formulation FA3 showed more than 75 % drug release within 5 minutes and more than 90 % drug release after 7.5 minutes. Marketed tablet showed 79.5 % drug release after 30 minutes. Thus, prepared liquisolid compacts showed higher drug dissolution rate than marketed tablet.

This observation could be explained according to the Noyes–Whitney equation and the diffusion layer model. In liquisolid system, drug is in solution form and the surface area of drug is increased. After disintegration of system, the primary particles are suspended in the dissolution medium containing drug particles which are in the molecular dispersion state. The marketed tablet showed lower drug release than the liquisolid compact due to the limited surface area exposed for dissolution.[15,16]

DE is commonly applied for comparison of dissolution profiles to decide better formulation. The marketed formulation showed 73.32% DE whereas the formulations (AA2, FA2, FA3, NAD2, NAD3, NND2 and NND3) showed more than 85% DE, at the end of 60 min. DE of optimized liquisolid formulation FA3 was found to be 94.32%. Higher DE indicated that liquisolid compact has significantly enhanced dissolution rate ($p< 0.05$) (Table 5).

MDT of marketed formulation was found to be 9.46 min while that of formulation FA3 was 4.09 min. Lower MDT values indicated faster release of drug from liquisolid formulation (Table 5).

Finally, on the basis of total drug release and drug release at 5 min, 10 min and 15min, tablet size, hardness, DE (%) and MDT, formulations FA3, NAD3 and NND3 showed promising *in vitro* results.

IR- spectroscopy

The FT-IR spectra of CBZ showed distinct peaks at 3470 cm^{-1} (NH_2), 1680 cm^{-1} (C=O), and 1600 cm^{-1} (aromatic C=C).[37] The FTIR spectra of liquisolid formula-

Table 5: DE and MDT of CBZ liquisolid compacts

Batch	Q5 (%)	Q15 (%)	DE (%)	MDT (min)
AA1	40.21	58.84	60.37	10.58
AA2	65.13	80.25	86.37	7.81
AA3	35.13	68.19	77.4	12.89
FA1	45.51	63.51	68.32	13.21
FA2	67.90	88.09	90.16	6.51
FA3	78.98	99.92	94.32	4.09
NAD1	25.44	40.38	56.88	23.68
NAD2	30.46	87.4	85.97	9.10
NAD3	48.63	99.32	90.72	6.21
NND1	10.38	29.94	50.34	26.52
NND2	45.00	84.8	85.99	8.45
NND3	51.92	97.61	90.08	5.93
Tegretol	51.40	71.10	73.32	9.46

Q5-drug release at 5 min; Q15- drug release at 15 min;
DE- dissolution efficiency; MDT- mean dissolution time

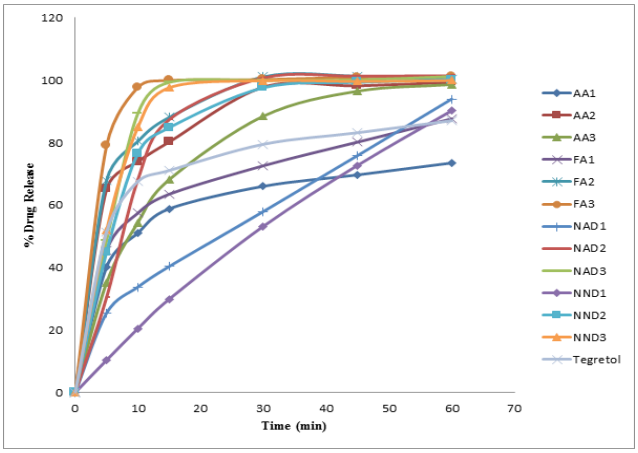

Figure 2. Dissolution profiles of liquisolid compact and marketed formulation

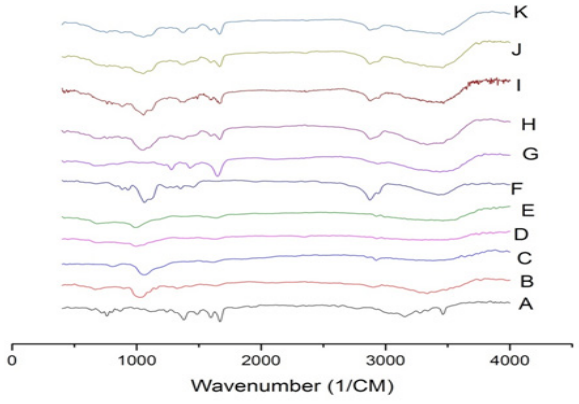

Figure 3: Overlay IR of carbamazepine (A), Avicel(B), Aerosil (C), Fujicalin(D), Neusulin (E), PEG 200(F), Cospovidone (G), Formulation AA2 (H), Formulation FA3 (I), Formulation NAD3 (J), Formulation NND2 (K)

tions AA2, FA3, NAD3, NND2 showed characteristic distinct peaks of Avicel 102, Fujicalin, Neusilin, and CBZ with approximately same intensity. Thus, there is no undesired interaction between the drug and ingredients. As shown in Figure 3, there is reduction in intensity of the characteristic absorption bands of CBZ in liquisolid formulations which might be attributed to the hydrogen bonding interaction of the amino and carboxyl group of CBZ with hydroxyl group of the liquid vehicles.[38] This resulted in drug dissolution enhancement as shown by dissolution data.

X-ray powder diffraction

It has been shown that polymorphic changes of the drug are important factors that may affect the dissolution rate and bioavailability. It is therefore important to study the polymorphic changes of the drug. X-ray diffraction pattern is given in Figure 4. XRD pattern of CBZ indicates drug is in its crystalline state. It was determined by characteristic intense XRD pattern with peaks at 2θ angle 12.96, 15.28, 19.80, 24.47 and 26.95.[29] On the other hand, the liquisolid powder XRD pattern of AA2 batch (Figure 4) showed diffraction peak at 2θ angle of 22.48 belonging to Avicel 102,[39,40] indicating that only Avicel102 maintained its crystalline state. Such absence of CBZ constructive reflections (specific peaks) in the liquisolid X-ray diffractogram indicates that drug has almost entirely converted from crystalline to amorphous or solubilized form, such lack of crystallinity in the liquisolid system was understood to be as a result of CBZ solubilization in the liquid vehicle that was absorbed into and adsorbed onto the carrier material (Avicel 102) and coated with the coating (Aerosil 200). It was also found that X-ray diffraction pattern of FA3, NND2, NAD3 indicated absence of CBZ constructive reflections (specific peaks) in liquisolid. X-ray data supported the conclusion that the CBZ formed a

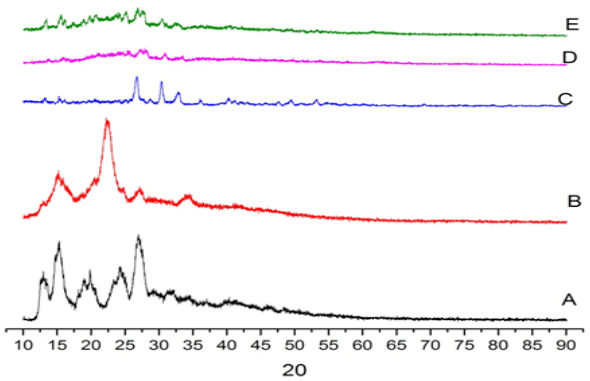

Figure 4 . Overlay XRD of carbamazepine (A), Formulation AA2 (B), Formulation FA3 (C), Formulation NAD3 (D), Formulation NND2 (E)

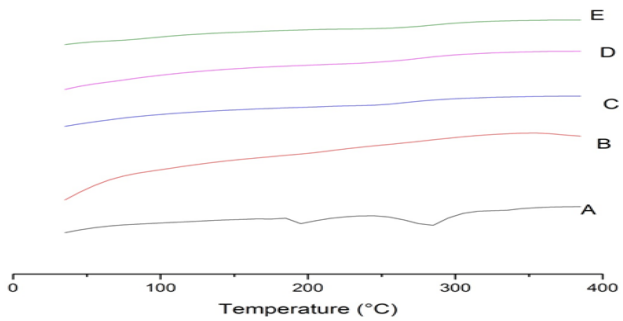

Figure 5: Overlay DSC of carbamazepine (A), Formulation AA2 (B), Formulation FA3 (C), Formulation NAD3 (D), Formulation NND2 (E)

solid solution within the carrier matrix. This amorphization or solubilization of CBZ in the liquisolid system may contribute to the consequent improvement in the apparent solubility and therefore the dissolution rate of CBZ.

Differential Scanning calorimetry

The DSC thermogram of the drug (A) in Figure 5 depicts a sharp endothermic peak at 289°C corresponding to the melting temperature of CBZ. Such sharp endothermic peak signifies that CBZ used was in pure crystalline state. The thermogram of liquisolid formulation did not show any additional peaks which indicate lack of unusual interaction between CBZ and excipients. DSC thermogram of liquisolid formulation AA2, FA3, NAD3, NND2 has displayed complete disappearance of characteristic peak of CBZ. This may be due to the formation of drug solution in the liquisolid powdered system, i.e. the drug was molecularly dispersed within the liquisolid matrix.[41]

CONCLUSION

The results indicated that despite of high dose, the liquisolid compacts of CBZ can be prepared using the novel carriers like Neusilin and Fujicalin and non volatile solvent like PEG. Fujicalin and Neusilin showed great potential to load the non-volatile solvent while maintaining good flow properties and helped to reduce the total tablet weight. The liquisolid formulations containing novel carriers showed improved dissolution than the marketed tablet of CBZ. The formulation FA3 showed lower MDT and high dissolution efficiency than the other formulations. The novel porous carriers were found to be superior to Avicel for loading high dose drugs like CBZ. Further studies with combining both Fujicalin and Neusilin together in varying ratios are required for better results.

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CONFLICT OF INTEREST

We have no conflict of interest to declare.

ABBREVIATION USED

ATR: attenuated total reflectance; CBZ: carbamazepine DE: dissolution efficiency; DSC: differential scanning calorimetry; MDT: mean dissolution time; PEG: polyethylene glycol; SSA: specific surface area; XRD: X-ray powder diffraction.

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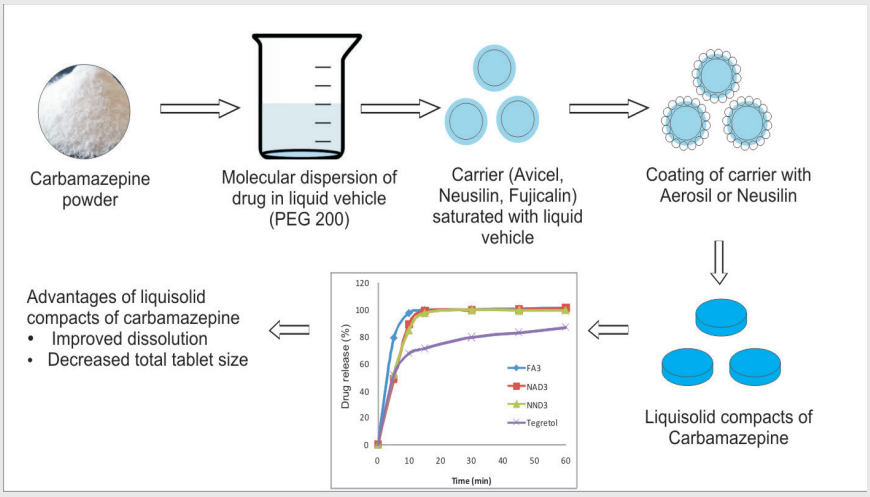
PICTORIAL ABSTRACT



SUMMARY

- Liquisolid compacts of high dose water insoluble drug carbamazepine (CBZ) was prepared using novel porous carriers such as Neusilin and Fujicalin in order to improve its dissolution rate and reduce the tablet weight.
- It is very challenging to reduce total tablet size when traditional carrier Avicel is used.
- CBZ showed greater solubility in liquid vehicle- polyethylene glycol 200.
- Carriers like Neusilin and Fujicalin showed high capacity to load large quantity of liquid than the traditional carrier Avicel.
- Solid state characterization of liquisolid compacts revealed amorphization of CBZ.
- Liquisolid compacts formulated with Fujicalin showed improved dissolution of CBZ than marketed formulation.
- The novel porous carriers were found to be superior to Avicel for loading high dose drugs like CBZ and reduce total tablet weight.

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