Emerging Liquisolid Compact Technology for Solubility Enhancement of BCS Class-II Drug

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Abstract:

Diazepam possesses potent anti-epileptic, anti-anxiety activity and also indicated for the treatment of insomnia. It is very slightly soluble in water and shows poor dissolution. Presently, liquisolid compact technique is found to be used extensively as one of the successful tool to enhance the solubility and dissolution of various poorly soluble drugs. The principle focus of this study is to formulate Liquisolid compacts of Diazepam to enhance its dissolution rate. Here, liquisolid compacts are fabricated using different non-volatile solvents and converting them into acceptably flowing and compressible powders for efficient compact tablet production. The solubility studies are carried by dispersing the drug in various dissolution enhancing agents (non- volatile solvents) such as Polyethylene glycol 400 (PEG-400), Polyethylene glycol 600 (PEG-600), Propylene glycol, Tween 80, Span 80 and Glycerol. The drug solubility is comparatively high in PEG-600, which is selected as suitable vehicle for the formulation and its further study. The formulations are made by using different ratios of Drug and PEG-600, then by the addition of diluents like manitol, microcrystalline cellulose (Avicel pH-101) and lactose as carrier materials and other excipients to optimize the direct compression process. The prepared blends are subjected to the pre-formulation studies and the compressed liquisolid compacts are evaluated for the physical parameters such as uniformity of weight, hardness, diameter, thickness, friability, disintegrention, content uniformity and *in-vitro* dissolution. The FTIR and DSC analysis are performed to confirm the compatibility and stability of the drug with the excipients.

Key words: Diazepam, Dissolution enhancement, PEG, Poorly soluble drugs

INTRODUCTION

The solubility of many active pharmaceutical ingredients is one of the technical challenge in formulating as suitable dosage form for efficient its drug delivery. Most of the hydrophobic drugs termed as sparingly soluble, slightly soluble and very slightly soluble, undergoes very poor dissolution in the gastro intestinal tract, leading to erratic and incomplete absorption. For these drugs, the dissolution process is the rate-controlling step, which determines the rate and degree of its absorption. Nearly 40% - 50% of newly developed and orally administered drugs exhibit solubility problem in aqueous media due to its high lipophilicity, which directly reflects in the difficulty in formulation development of those drugs.

Even though oral route is the most preferred route for drug administration due to its fulfillment of necessary strategies for drug development and patient acceptance, the poorly soluble drugs generally exhibit slow dissolution rates and incomplete bioavailability due to poor wettability in the gastro intestinal tract (GIT). The drugs belonging to the biopharmaceutical classification system (BCS) class II and IV dissolve slowly, poorly or irregularly, which results in incomplete release of the drug from the dosage form, increase in the dose, large inter and intra-subject variation in blood drug concentrations under fed and fasted conditions ultimately leading to poor bioavailability [1-3].

Over past few years, various formulation techniques have been developed, to improve the solubility and dissolution of poorly soluble substances, with different degrees of success. There are multiple methods which have been used for past many years, to enhance the dissolution characteristics of water insoluble drugs which includes micronization, lyohilization, solid dispersion etc [4-6]. Out of which the recent research focus on liquisolid compact technique as one of the successful tool to achieve the goal.

Liquisolid compacts are acceptably flowing and compressible powder forms of liquid medications. The liquid medication is the water insoluble drugs carried in suitable non-volatile solvents. This liquid medication is converted into a free flowing powder by addition of suitable excipients. The concentrations of the carriers, coating materials,

disintegrants, lubricants and glidants are optimized to get a non-sticky easily compressible blend. This technology ensures the promotion of dissolution rate of poorly water soluble drugs since the drugs are completely solubilised in the suitable solvents before converting it into free flowing mass [7, 8].

The drug in the solid dosage form is held within the powder substrate in a solution or in a solubilized, almost molecular dispersion level, which is the main reason for its significant change in the wetting properties and effective surface area. The drug available for dissolution is increased and hence show enhanced drug release characteristics and improved oral bioavaibility.

The carrier and coating powder material can retain only certain amounts of liquid while maintaining acceptable flow and compression properties depending on the excipients ratio. The powder exicipent ratio R is the fraction of weight of carrier (Q) and the coating material (q) present in the formulation R= Q/q. The maximum liquid load on the carrier material is termed as the liquid load factor. Lf is defined as the weight ratio of the liquid medication (w) and carrier powder (Q) in the system Lf= w/Q, which must be posed by an acceptable flowing and compressible preparation. The φ-value of a powder is the maximum amount of a given non-volatile liquid that can be holded inside its bulk (w/w) while maintaining the reasonable flow. The ψ-number of a powder is the maximum amount of liquid that can be retained by a powder within its bulk (w/w) while maintaining acceptable compactability, so that while making cylindrical compacts with enough strength 'liquid-squeezing-out' phenomena does not occur. The φ-value and the ψ-number of powder may be determined using the procedure liquisolid flowability test (LSF) and liquisolid compressibility (LSC) test, respectively [9, 10].

The compaction techniques can be proceeded via direct compression method and slugging method [11-15]. The formulation of liquisolid compacts has several merits which includes simplicity, low cost and capability of industrial scale up production.

Diazepam is a potent anti-epileptic and anti-anxiety drug with narrow therapeutic index. Its poor solubility in water slows down the dissolution, leading to restricted absorption [16, 17]. The present work emphasis on the development of liquisolid compact formulation for this deserving drug candidate to enhance its solubility and dissolution, thereby increase its absorption in the GIT.

MATERIALS AND METHODS

MATERIALS:
Diazepam is obtained as gift sample from Ranbaxy Ltd, Mumbai, India. The non-volatile solvents such as Poly ethylene glycol (PEG 600 and PEG 400), Propylene glycol, Glycerol, Tween 80, Tween 20 and Span 20 are purchased form S.D. fine chem Limited, Mumbai, India. The carriers and other excipients such as Micro Crystalline Cellulose, Mannitol, Silicon dioxide, Lactose monohydrate, Sodium Starch Glycollate, Aerosil 200, Talc fine powder, Magnesium stearate are purchased from Loba Chemie, Mumbai, India.

METHODOLOGY:
Physical characterization of API: [18-20]
Diazepam pure drug powder is evaluated for its physical properties such as appearance (colour, odour, etc), solubility, angle of repose, bulk density, tapped density, compressibility index and hausner ratio.

Solubility studies: [1, 3]
Solubility studies of diazepam are carried out in different non-volatile solvent such as Polyethylene glycol 600, Polyethylene glycol 400, Propylene glycol, Glycerol, Tween 20, Tween 80 and Span 20. Saturated solutions are prepared by adding weighed quantity of excess amount drug to the vehicle and dissolving using the orbital shaker (Khera, Bombay, India) for 24 hours at room temperature under constant vibration. After this period, the solution is centrifuged (Centrifuge apparatus, Remi, Bombay). Accurately measured quantities of the supernatant solution is filtered and are further diluted with methanol and analyzed spectrophotometrically using UV-Visible spectrophotometer (Perkin Elmer precisely lambda 25) at λmax of Diazepam (241 nm) to determine the amount of drug dissolved in it.

Estimation of holding capacity and loading factor of the excipients: [9, 10]
It is the capacity of an excipient to hold liquid and behave like dry powder. 0.5 ml of the non-volatile solvent is accurately measured and transferred to a clean dried mortar. The carrier and coating materials such as MCC, aerosil 200, silicon dioxide, mannitol and lactose are sifted using sieves (M.B. Instruments, Delhi) with mesh no: 44 (BSS/ASTM), then added in successive quantities to the solvent (added to separate solvent individually) and the mixture is blended after each addition to help distributing the liquid throughout the powder particles. The addition of powder and mixing is continued until mortar contents start to look like dry

free flowing powder. The holding capacity for each excipient is estimated individually.

Evaluation of flowability and compressibility of liquisolid powder: [7, 10]

The flowability of the mixtures is calculated by measuring the angle of repose for each exicipients and for combination of exicipents. Determination of bulk and tap density is used to calculate both the Hausner ratio and the Carr's index.

Differential scanning calorimetry (DSC): [21]

The physicochemical compatibilities and polymorphic changes of the drug and excipients are tested by differential scanning calorimetric analysis (DSC Q20 TA instrument). DSC is performed by accurately weighing about 2 mg of the samples of pure drug and liquisolid compacts placed in aluminum pans and the empty pan are also sealed which are used as reference. The instrument is calibrated using indium as the standard. Thermal behavior of the sample is investigated at a scanning rate of 140^oC min^{-1}, covering a temperature range of 0 to 200^oC.

X-Ray Diffraction Studies: [22]

The crystalline morphology of Diazepam and the selected formulation are analysed by powder X-Ray Diffractometer (Brukker, USA) with Cu Kα radiation, in the range of $2\theta = 20$-60° at slow angle scan of 0.01^o/min.

Formulation development: [9, 10, 14]

The specific quantity of drug is dispersed in the non-volatile solvent and dissolved using the orbital shaker for 24 hours at room temperature under constant vibration. Based on the solubility studies, PEG 600 is selected as suitable non-volatile solvent for required quantity of Diazepam. The carriers and coating materials are sifted through sieve no: 44 (BSS/ASTM) and added in various concentrations and mixed for 10 minutes, to convert the liquid into dry-looking, non-adherent, free flowing powder. The blend is pre-compressed and slugged. The slugged material is sifted through sieve no: 22 (BSS/ASTM) to get uniform granules. It is then directly compressed into tablets using single punch tablet compression machine (KI-150 Khera Instruments Ltd, New Delhi, India) using 8.5 mm deep concave punches with suitable compression force.

The trial-I formulations (F-1 to F-4) are made using microcrystalline cellulose and aerosil 200 as carriers and sodium starch glycolate as super disintegrants. In trail-II study, (F-5 to F-8) microcrystalline cellulose, lactose monohydrate and mannitol are added as carriers and sodium starch glycolate as super disintegrants. Due to poor flow of the formed blend, talc and magnesium stearate are added as lubricants. In trial-III preparations (F-9 to F-11), microcrystalline cellulose and silicon dioxide are added as carriers and sodium starch glycolate is added for disintegration.

Pre-compression studies of liquisolid compacts: [19, 20]

The blend material ready for compression is evaluated for the pre-compression parameters such as bulk density, tapped density (Tapped density apparatus, Labindia, Mumbai, India), angle of repose (Funnel method), flow and compressibility (compressibility index or Carrs index and Hausners ratio)

Physical evaluation of liquisolid compacts: [20, 23]

The compressed liquid solid compacts are evaluated for the uniformity of weight of the individual tablets using electronic weighing balance (Model no: BL 220H, Schimadzu corporation, Japan). The hardness of the compacts is measured using Monsanto hardness tester (Cadmach, Ahemdabad, India) and the dimensions (thickness and diameter) are measured by vernier caliper (Mitutoyo, Japan). The percentage friability is evaluated using the Roche friability test apparatus (Veego, Mumbai, India). The disintegration time is detected by the tablet disintegration test apparatus (Labindia, Mumbai, India).

Estimation of drug content: [23]

The liquisolid compacts are powdered well and powder equivalent to 10 mg of the drug is accurately weighed and suitably diluted using methanolic sulphuric acid. The drug content is calculated by measuring the absorbance of the solution at wavelength of 284nm using UV-Visible spectrophotometer.

***In-vitro* drug release study: [23, 24]**

The *in-vitro* dissolution study is carried out for a period of 1 hour using USP XXIV type-II (paddle) method with 900 ml of 0.1 N HCl and distilled water as the dissolution media at 100 rpm and 37^oC $\pm 0.5^o$C. 10 ml of the sample is withdrawn and filtered at periodic time intervals of 5, 10, 15, 30, 45 and 60 minutes. 10ml of fresh dissolution fluid is replaced to the baskets to maintain the constant volume (sink condition). The filtered samples are analyzed at 241nm by UV/Visible spectrophotometer. The mean of n=3 determinations is used to calculate the percentage drug release from each formulation.

RESULTS AND DISCUSSION

Pre-formulation and Solubility studies:

Diazepam is a white solid crystal with slightly bitter taste. It is poorly soluble in water, soluble in alcohol and freely soluble in chloroform. The bulk and tapped density of the pure drug is 0.4879 and 0.8695 gm/ml respectively. Diazepam has poor flow and compressibility (Angle of repose 43.4˚, Cars index 48.79 and Hausner's ratio 1.78), which indicates the need of the suitable concentrations of directly compressible excipients and glidants to optimize the formulation. Based on the solubility studies preformed using different non-volatile solvents such as PEG 600, PEG 400, Propylene glycol, Glycerin, Tween 20, Tween 80, Span 20 the results show that PEG 600 is suitable for the formulation of liquisolid compacts of Diazepam (due to its highest solubility of 44.97% as shown in Table 1

Table: 1 Solubility studies of Diazepam in different non-volatile solvents

S. No.	Non-volatile Solvents	% Drug Solubility
1.	Polyethylene glycol 600	44.97
2.	Polyethylene glycol 400	41.36
3.	Propylene glycol	16.27
4.	Glycerin	2.099
5.	Tween 20	35.90
6.	Tween 80	33.47
7.	Span 20	16.596

Estimation of Loading factor and Flowability:

The loading factor and angle of repose is estimated for the liquid-carrier mixture to find its suitability and flowability to compress into compacts. Aerosil 200 (Lf=1.85) and silicon dioxide (Lf=3.70) shows minimum loading factor and good flow property (angle of repose 25 to 35˚). Comparison of the loading factor value of all the excipients shows that the mixture of excipients in suitable ratios can result in optimum formulation. (Table 2)

Table: 2 Loading factor and Flow property of different excipients

S. No.	Excipients	Loading factor (Lf)	Angle of repose (θ)
1.	Microcrystalline cellulose	12.96	52.87±4.12
2.	Lactose	16.6	42.15±2.66
3.	Mannitol	22.2	37.41±4.25
4.	Aerosil 200	1.85	29.38±2.99
5.	Silcon dioxide	3.7037	33.96±1.31

Differential scanning calorimetry:

The DSC spectrum of Diazepam shows sharp endothermic peak at 136˚C which is the identity for melting point of drug. (Figure 1) The DSC spectrum of the selected formulation also shows similar peak (Figure 2) which proves that there is no possible physical or chemical interaction between the drug and exicipients.
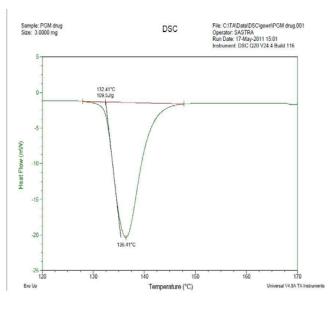

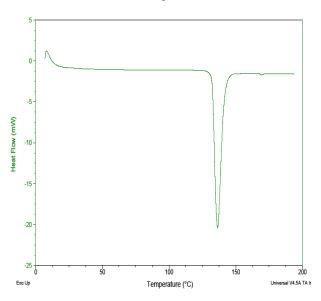**Figure: 1** *DSC thermogram of pure Diazepam sample*

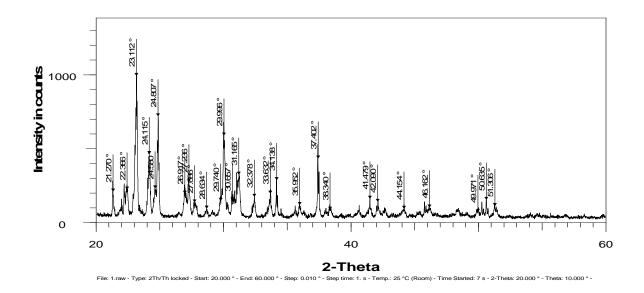**Figure: 2** *DSC thermogram of selected liquisolid compact formulation*

File: 1.raw - Type: 2Th/Th locked - Start: 20.000 ° - End: 60.000 ° - Step: 0.010 ° - Step time: 1. s - Temp.: 25 °C (Room) - Time Started: 7 s - 2-Theta: 20.000 ° - Theta: 10.000 ° -

Figure: 3 *XRD spectrum of pure Diazepam sample*

File: 2.raw - Type: 2Th/Th locked - Start: 20.000 ° - End: 60.000 ° - Step: 0.010 ° - Step time: 1. s - Temp.: 25 °C (Room) - Time Started: 7 s - 2-Theta: 20.000 ° - Theta: 10.000 ° -
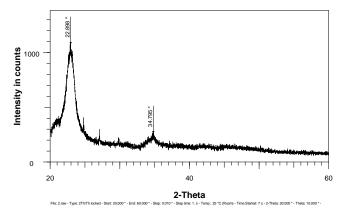
Figure: 4 *XRD spectrum of selected liquisolid compact formulation*

X-Ray Diffraction:
The XRD spectrum of the pure drug (Figure 3) shows more number of sharp peaks indicating its highly crystalline morphology, whereas the optimized liquisolid compact formulation (Figure 4) indicates only very few peaks at 2θ of 22.898 and 34.795. The disappearance of 2θ angles in the liquisolid compact formulation is evident that crystalline pure drug is converted into amorphous state due to its molecular solubilization of the drug in the non-volatile solvent, which proves the enhancement of solubility by this technique.

Formulation of Liquisolid mixtures:
The trial-I formulations (F-1 to F-4) are formulated by changing the concentration of drug and sodium starch glycolate. The trial-II formulations (F-5 to F-8) are prepared by fixing microcrystalline cellulose, lactose and mannitol at same ratio and changing the concentration of drug, sodium starch glycolate and aerosil as variables. In trial-III formulations (F-9 to F-11) microcrystalline cellulose, silicon dioxide, sodium starch glycolate are at fixed concentrations but amount of drug dissolved is the variable. The liquisolid powder mixture is compressed by slugging method and then again sieved to get uniform size granules. The yield of the mixture is calculated and the weight of each tablet is fixed to get a label claim of 2.5 mg dose of the drug (Table 3).

Table: 3 Composition of Diazepam liquisolid compacts

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
Diazepam (g)	0.050	0.025	0.050	0.075	0.050	0.025	0.050	0.075	0.025	0.050	0.075
PEG-600 (ml)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
MCC (g)	5.0	5.0	5.0	5.0	2.5	2.5	2.5	2.5	3.0	3.0	3.0
Aerosol200 (g)	0.25	0.25	0.25	0.25	0.15	0.16	0.16	0.16	-	-	-
SSG (g)	0.26	0.39	0.39	0.39	0.39	0.56	0.56	0.56	0.24	0.24	0.24
Lactose (g)	-	-	-	-	2.5	2.5	2.5	2.5	-	-	-
Mannitol (g)	-	-	-	-	2.5	2.5	2.5	2.5	-	-	-
Silicon dioxide (g)	-	-	-	-	-	-	-	-	0.25	0.25	0.25
Talc (g)	-	-	-	-	0.075	0.08	0.08	0.08	-	-	-
Magnesium stearate (g)	-	-	-	-	0.15	0.16	0.16	0.16	-	-	-
Total yield (g)	5.562	5.672	5.697	5.722	8.321	8.204	8.522	8.548	3.515	3.543	3.568
Weight per Tablet (g)	0.278	0.567	0.284	0.190	0.416	0.820	0.426	0.284	0.351	0.177	0.118

PEG – Poly Ethylene Glycol, MCC – Micro Crystalline Cellulose, SSG – Sodium Starch Glycollate, g – gram

Table: 4 Granular characterization of the liquisolid mixture

Formulation	Angle of repose (^{o}) *	Bulk density (g/ml) *	Tapped density (g/ml) *	Hausner ratio	Carr's index
F-1	33.21±2.0	0.389±0.9	0.524±0.2	1.347	29.19
F-2	29.4±1.2	0.384±0.6	0.555±0.3	1.445	30.81
F-3	34.31±0.8	0.465±0.8	0.95±0.98	2.043	51.05
F-4	32.0±0.2	0.454±0.6	0.90±0.56	1.98	49.55
F-6	33.36±0.3	0.500±0.8	1.25±0.9	2.5	60.0
F-7	29.59±1.1	0.479±0.7	0.909±0.3	1.89	47.30
F-8	35.75±0.9	0.500±0.7	0.710±0.6	1.43	29.57
F-9	32.19±1.3	0.30±0.8	0.50±0.9	1.66	40.0
F-10	22.70±0.8	0.344±0.2	0.526±0.4	1.12	14.60
F-11	35.53±1.2	0.307±0.2	0.50±0.5	1.66	0.386

* Average value of n=3 readings

Characterization of granules:

The pre-compression evaluation of the formulations F-1 to F-11 reveals that formulation F-10 containing microcrystalline cellulose, silicon dioxide and sodium starch glycolate shows good flow property and compressibility (angle of repose 22.7, cars index 14.6, Hausner ratio 1.12) compared to other trials (Table 4). All other formulations show passable flow and compressibility.

Evaluation of Diazepam Liquisolid compacts:

The average weight of trail formulations F-1, F-2, F-3, F-5, F-6, F-7, F-8 and F-9 are greater than 250mg and formulation F-4, F-10, F-11 the average weight is less than 250mg, which is fixed based on the granules yield and Diazepam label claim dose. The individual weight variation of the tablets is within the standard limits of ±5% and ±7.5% respectively.

Formulations having the hardness of 0.5 and 1 kg/cm^2 show greater percentage friability, whereas formulations F-1 and F-10 shows hardness 3 – 4 kg/cm^2 with less friability. The formulation F-1 having hardness of 4 kg/cm^2 shows 7 minutes disintegration time. When the hardness was decreased to 3 kg/cm^2 in formulation F-19, the disintegration time is 1.5 minutes which is optimum for immediate release. The uniformity of drug content of all the trial formulations are found to be within the required limits (90-110%).

The pre-compression parameters, uniformity in weight, dimensions, hardness, disintegration time and drug content of formulation F-10 is found to be more satisfactory and optimum compared to other trails (Table 5)

Table: 5   Evaluation of Diazepam Liquisolid compacts

Formulation Code	Hardness (kg/cm^2)	Friability (%)	Disintegration time (mins)	Weight variation(mg)	%Drug content
F-1	4	0.003	7.20	0.2781±0.02	94.56
F-2	2	0.444	2.0	0.5672±0.04	92.87
F-3	2	0.177	7.0	0.2848±0.01	93.54
F-4	2	0.557	4.0	0.1907±0.02	99.32
F-5	1	0.006	2.0	0.4160±0.09	98.45
F-6	0.5	0.349	2.0	0.8204±0.02	103.56
F-7	1	0.191	50sec	0.4261±0.01	94.62
F-8	0.5	0.881	4.0	0.2849±0.02	107.65
F-9	1	0.002	1.0	0.3299±0.03	93.76
F-10	3	0.001	1.5	0.1771±0.01	98.54
F-11	1	0.004	2.0	0.1189±0.02	105.87

Figure: 5   Comparison of in-vitro release of liquisolid compacts with pure drug Using distilled water as dissolution media
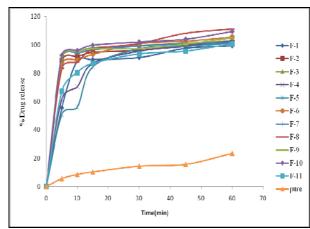

Figure: 6   Comparison of in-vitro release of liquisolid compacts with pure drug Using 0.1N HCl as dissolution media

In-vitro dissolution studies:

The *in vitro* release studies of all formulations are carried out for 1 hour using distilled water and 0.1N HCl individually to predict the aqueous solubility and the release pattern in the stomach pH, respectively.   The drug solubility and release is found to be greater than the pure drug in both media. The enhancement of solubility is observed in all the liquisolid compacts independent of the type of carriers used and its concentration. A profound markable enhancement of solubility of the drug is observed in distilled water as dissolution media. The pure drug shows 5.6% of drug release at 5 minutes in distilled water which increased gradually up to 23.41% at 60 minutes.   The liquisolid compacts (F-1 to F-11) showed enhanced solubility and dissolution upto the range of 50-90% drug release at 5 minutes and reaches the maximu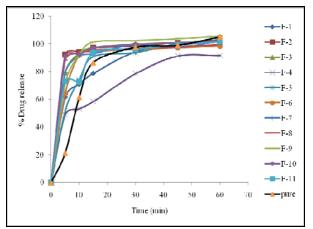m of 110% within 1 hour (Figure 5).   Similarly, while using 0.1N HCl as media, at 5 minutes, the pure drug release is 21.5% whereas formulation F-2 and F-10 shows more than 90% at the same time (Figure 6).

CONCLUSION

The solubility and dissolution of poorly soluble drug Diazepam is enhanced by the liquisolid compact technique. Various trials are characterized based on the pre-compression and post-compression parameters which showed formulation F-10 containing microcrystalline cellulose, silicon dioxide and sodium starch glycolate with Diazepam dissolved in PEG 600 as an optimized formula with required properties.   The *in-vitro* release studies performed using two different dissolution media distilled water and HCl also justifies the enhancement in solubility and dissolution compared to the pure drug

REFERENCES

[1] Yadav, V.B., Yadav, A.V., Journal of pharmaceutical sciences and research, 2009 , 1 (2), 44-51

[2] Bindu, M.B., Kusum, B., David Banji, International journal of pharmaceutical sciences review and research, 2010, 4(3), 76-84.

[3] Spiro spireas, Srinivas Sadu, Int.J.Pharma, 1998, 166, 177-188

[4] Anil J Shinde, Pharmainfo.net, 2007

[5] Rajinipharma, Pharmainfo.net, 2009

[6] Betageri, G.V., Makarala, K.R., Int. J. Pharma, 1995, 126, 155-160

[7] Babatunde, A., Elkordoy, A. A., Esse, E. A., Elhagar, S., Scientia pharmaceutica, 2010, 78, 325-344

[8] Yadav, A.V., Shete, A.S., Dabke, A.P., Indian J. Pharm. Educ. Res., 2010, 44(3), 227-235

[9] Gubbi, S.R., Jarag, R., Research J. Pharm. and Tech., 2009, 2(2), 382-386

[10] Elsay, K.M., Samy, A. M., Fetouh, M.I., International journal of pharmaceutical sciences review and research, 2010, 3(1), 135-142

[11] Sandeep, G., Rangasamy, M., Journal of Pharmacy research, 2009, 2(4), 619-621

[12] Deshmukh, V.N., Sing, S.P., Sharkarkar, D.M., International journal of pharmatech research, 2009, 1(2), 159-163

[13] Liberman, H.A., Leon Lackman, Schwartz, J.B., (2nd ed) Pharmaceutical dosage forms, Tablets (Volume-I), 1989, Informa healthcare, pp. 228-229, 476-478, 486-487.

[14] [Jivraj, M., Martini, L.G., Thomson, C.M., Pharm Science Technology Today, B.F. Goodrich Bulletin, 2003, 3, 58-63.

[15] Panna Thapa, Manish Ghimire, Alex, B., Mullen, Stevens, H.N.E., Kathmandu university journal of science, engineering and technology, 2005, 1(1), 1-10

[16] [Malgorzata Sznitowska, Monika Gajewska, Stanislaw Janicki, Aleksandra Radwanska, Gerold Lukowski, European journal of pharmaceutics and biopharmaceutics, 2001, 52, 159-163

[17] http://www.mims.com/USA/drug/info/diazepam

[18] Ramya devi, D., Gopinath, V., Vedha Hari, B.N., Indian Journal of natural sciences, 2010, 1(1), 35-40

[19] Remington, Lippincot Williams, Wilkins, (21st ed), The science and practice of pharmacy, 2000, pp. 939-964

[20] Leon Lachman, Lieberman, H.A., Kanig, J.L., The theory and practice of industrial pharmacy, Varghese publishing house, 1991, pp. 183-184, 297-299

[21] Vedha Hari, B.N., Samyuktha Rani, B., Inventi Rapid Pharma. Tech., 2010, 1(2), 1-6

[22] Gubbi, S.R., Ravindar Jarag, Asian journal of pharmaceutical sciences, 2010, 5(2),50-60

[23] Indian Pharmacopeia, Vol-I and II Indian Pharmacopeia Commission, Ghaziabad, Govt. of India: Ministry of Health and Family Welfare, 2007.

[24] United States Pharmacopoeia Vol. I – II (USP 32 Revision and NF 27 edition USP NF 2009)