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Formulation and Evaluation of Fast DisintegrationTablets of Clonazepam

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ABSTRACT

Recent development in Fast disintegration tablets have brought convenience in dosing to elderly and children who have trouble in swallowing tablets. The objective of the present study was to prepare the Fast disintegration tablets of clonazepam, an antiepileptic drug. As precision of dosing and patient compliance become an important prerequisite for a long term antiepileptic treatment, there is a need to develop a formulation for this drug which overcomes problems such as difficulty in swallowing, inconvenience in administration while travelling and patient's acceptability. Hence, the present work was undertaken with a view to develop a fast disintegration tablet of clonazepam which offers a new range of product having desired characteristics and intended benefits. Various techniques like spray drying, direct compression and sublimation technique were used to formulate Fast disintegration tablets of clonazepam. In direct compression method the effect of addition of spray dried excipients was studied, crospovidone was selected as superdisintegrant in all the techniques. A 2^2 factorial design was employed in all the approaches to study the effect of variables. The tablets were evaluated for hardness, friability, weight variation, wetting time, disintegration time and uniformity of content. Optimized formulations were evaluated for *in-vitro* dissolution test. Amongst all the techniques sublimation technique was found to be most successful and tablets prepared by this technique (F13) had disintegration time of 4±0.8 sec. and %CR 65.2±1.52 after 5 min. But the results of this technique was almost similar to that of direct compression by using spray dried lactose (F10) which showed disintegration time of 4±0.5 sec. and %CR 64.1±0.14 after 5 min. Hence it was conclude that direct compression using spray dried excipients was simple and economic technique which can be used for formulation of Fast disintegration tablets of clonazepam.

KEYWORDS: Clonazepam, superdisintegrants, Direct compression technique, Sublimation technique and spray drying technique, Mouth disintegration tablets.

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INTRODUCTION

Fast disintegrates of tablet takes place when placed on tongue, releasing the drug that dissolves or disperses in the saliva[1]. A novel application of polymer processing technology to prepare pharmaceutical dosage forms now a day used. The process involves embedding a drug in a polymeric carrier while shaping the composite material to form a pharmaceutical product[2]. To fulfill these requirements, pharmaceutical technologists have developed a novel oral dosage form known as Orally Quick Disintegrating (ODTs) tablets which disintegrate rapidly in saliva, usually in a matter of seconds, without the need of water[3]. Clonezepam analysed both liquid–liquid (LLE) and solid phase extraction techniques (SPE).[4-6] Instrumental methods of analysis have employed gas chromatography[7], with prior derivatization,[8] high performance liquid chromatography[9] with mass spectrometry[10]. Gas chromatography/mass spectrometry using chemical derivatives such as BSTFA[11] and HFBA[12] also reported. The method presented in this paper employs MTBSTFA as the derivatizing agent for GC–MS (SIM). Previous animal studies have reproduced clonazepam drug as depression- like behavioral changes seen in humans.[3,14]

METHODOLOGY AND METHOD

Material required in the experiment are:- Clonazepam, Polyvinyl pyrrolidone K 30, Microcrystalline Cellulose, Crospovidone and Magnesium stearate,

Procedure

50 mg of Clonazepam was accurately weighed and dissolved in 50 ml methanol to get a stock solution of 1 mg/ml. Further, an aliquot was pipetted out and diluted suitably to get the concentration in the Beer's range. The aliquot was scanned in the wavelength region of 250-350 nm to record the wavelength of maximum absorption (λmax).

Preparation of standard stock solution:

50 mg of Clonazepam was accurately weighed and dissolved in small quantity of methanol by shaking the volumetric flask continuously on a cyclomixer for about 10 minutes. The volume was made up to 50 ml with methanol to get a stock solution of 1 mg/ml.

Preparation of working standard solution:

2ml of stock solution was further diluted to 100 ml with degassed water to produce a solution with a concentration of 20 g/ml. Using this solution, concentrations of 2 to 10 g/ml were prepared with degassed water. Drug excipient interaction study done.[15-17]

Formulation Of Fast Disintegration Tablets: By Spray Drying Technique:

Since the dose of the drug was less (0.5 mg) drug alone with lactose was used for spray drying to get a bulk product. The parameters were varied to get a free flowing product with less moisture and a good yield. The following trials were performed using spray dryer which shown in Table 5.

Table 1: Various parameters to be considered in operating a spray dryer

Parameters	T1	T2	T3	T4	T5	T6	T7	T8	Trial 9	Trial 10	Trial 11	Trial 12	Trial 13
Spray concentration	20%	20%	20%	20%	20%	20%	20%	20%	20%	20%	20%	20%	20%
Inlet temperature	60^0C	75^0C	85^0C	90^0C	102^0C	105^0C	110^0C	125^0C	60^0C	60^0C	60^0C	65^0C	65^0C
Outlet temperature	40^0C	60^0C	70^0C	75^0C	85^0C	95^0C	95^0C	110^0C	40^0C	40^0C	40^0C	55^0C	45^0C
Aspiration speed	60	70	70	60	60	70	60	55	65	65	65	60	65
Feed rate	10	08	08	08	06	07	10	06	10	08	09	06	10

Since it was not possible to get the required product with the alone trials, lactose was replaced by PVP-30and the following trials were performed which shown in Table 6.

Factor A: Numerical: Concentration of disintegrating agent (crospovidone).

Factor B: Numerical: Concentration of Microcrystalline Cellulose (MCC)

Table 2: Actual and coded levels of the factors

Factor	Actual values		Coded values	
	Low level	High level	Low	High
Factor A (Crospovidone)	2%	10 %	- 1	+ 1
Factor B (MCC)	5%	20%	- 1	+ 1

Table 3: Formulation

formulation	Clonazepam + PVP K30.		Micro crystalline cellulose.		Crospovidone.		Magnesium stearate.		Lactose.	
	Qty per tablet (mg)	Percentage (%)	Qty per tablet (mg)	Percentage (%)	Qty per tablet (mg)	Percentage (%)	Qty per tablet (mg)	Percentage (%)	Qty per tablet (mg)	Percentage (%)
F1	5.63	5.63	5	5	2	2	1	1	86.37	86.37
F2	5.63	5.63	5	5	10	10	1	1	78.37	78.37
F3	5.63	5.63	20	20	2	2	1	1	71.37	71.37
F4	5.63	5.63	20	20	10	10	1	1	63.37	63.37

By Direct Compression:

Tablets were prepared by direct compression method. All excipients were screened through #44 sieve and weighed individually. The weighed powder was compressed into tablet by using 6.7 mm round flat punches. A 2^2 full factorial design was used to formulate the tablets. The design consists of two factors at two levels.

Factor A: Numerical: Concentration of disintegrating agent (crospovidone).

Factor B: Numerical: Concentration of Microcrystalline Cellulose (MCC)

Table 4: Actual and coded levels of the factors

Factor	Actual values		Coded values	
	Low level	High level	Low	High
Factor A (Crospovidone)	2%	5 %	- 1	+ 1
Factor B (MCC)	5%	40%	- 1	+ 1

Table 5: Formulation

formulation	Clonazepam + PVP K30.		Micro crystalline cellulose.		Crospovidone.		Magnesium stearate.		Lactose.	
	Qty per tablet (mg)	Percentage (%)	Qty per tablet (mg)	Percentage (%)	Qty per tablet (mg)	Percentage (%)	Qty per tablet (mg)	Percentage (%)	Qty per tablet (mg)	Percentage (%)
F5	0.5	0.5	**5**	**5**	**5**	**5**	**1**	**1**	88.5	88.5
F6	0.5	0.5	**5**	**5**	**40**	**40**	**1**	**1**	53.5	53.5
F7	0.5	0.5	2	2	40	40	1	1	56.5	56.5
F8	0.5	0.5	2	2	**5**	**5**	**1**	**1**	91.5	91.5

EVALUATION OF FAST DISINTEGRATION TABLETS:

Pre-compression parameters are Determination of density, Percentage compressibility or Carr's index, Hausner ratio, Angle of repose.

TABLET PROPERTIES OF FAST DISINTEGRATION TABLETS:

The prepared tablets were evaluated for Thickness, Hardness, Friability, Weight variation, Disintegration test, Wetting time, Drug content, In-vitro dissolution studies.[15,16]

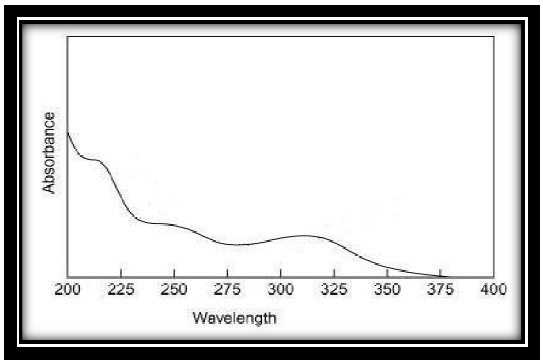

Figure 1: UV Spectrum of Clonazepam in Degassed water

Calibration curve of Clonazepam:

The absorbance value obtained for various concentration of clonazepam is tabulated in Table 31.

The calibration curve for Clonazepam in Degassed water was found to be linear with R^2 value 0.999 as shown in Fig.4.

Table 6. Data for calibration curve of Clonazepam in Degassed water.

Concentration in µg/ml	Absorbance* (mean ± SD)
0	0
2	0.064±0.003
4	0.126±0.003
6	0.189±0.003
8	0.255±0.004
10	0.320±0.002

*Average of three reading

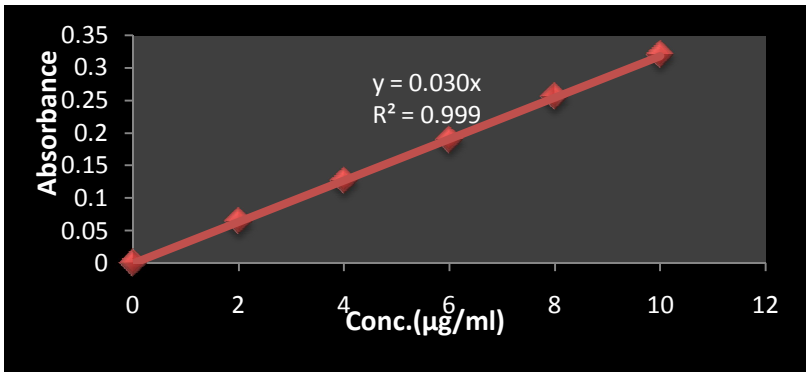

Figure 2: Calibration curve of Clonazepam

Pre-compression parameters:

The blend was evaluated for Poured density, tapped density, Carr's index, Hausner ratio and angle of repose and results are shown in Table 32.

Table 7. Results of pre-compression parameters of Formulations (F1-F4).

Formulation	Poured Density* (gm/ml^3)	Tapped density* (gm/ml^3)	Carr's index (%)	Hausner ratio (%)	Angle of repose* (degree)	Thickness* (mm)	Hardness* (Kg/cm^2)	Friability (%)	Disintegration time* (sec) (sec)	Wt. variation	Wetting time* (sec)	Drug content
F1	0.48	0.57	15.78	1.18	23°62'	2.3±0.06	4.5±0	0.23	360±0.240	PASS	420±0.279	94.00
F2	0.50	0.57	12.28	1.14	25°34'	2.3±0.05	4.5±0.204	0.18	81±0.040	PASS	54.5±0.262	96.56
F3	0.54	0.64	15.62	1.19	27°14'	2.3±0.03	4.5±0	0.24	355±0.376	PASS	360±0.269	94.62
F4	0.52	0.60	13.33	1.15	26°56'	2.3±0.02	4.5±0.204	0.27	90±0.038	PASS	65±0.084	95.49

Table 8. *In-vitro* dissolution data of F2 and F5.

Time (min)	% CR* F2	% CR* F5
0	0	0
5	47.2±1.10	59.2±1.13
10	55.6±1.81	65.5±0.12
15	71.9±0.62	71.3±1.19
30	83.25±0.75	77.05±0.75
45	100±0.09	87.95±1.09

* The values represents mean±SD, n = 3

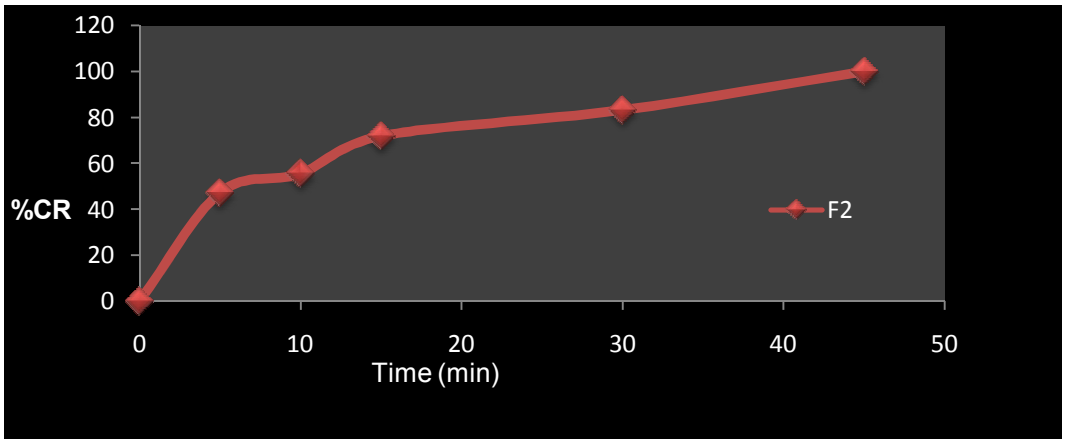

Figure 3: *In-vitro* dissolution profile of F2

Table 9: Parameter

Formulation	Poured Density* (gm/ml^3)	Tapped density* (gm/ml^3)	Carr's index (%)	Hausner ratio (%)	Angle of repose* (degree)	Thickness* (mm)	Hardness* (Kg/cm^2)	Friability (%)	Disintegration time*(sec) (sec)	Wt. variation	Wetting time* (sec)	Drug content
F5	0.57	0.67	14.92	1.18	27° 21'	2.3±0.01	2±0	0.19	8.7±1.082	PASS	13±0.09	97.30
F6	0.49	0.58	15.51	1.18	25° 96'	2.3±0.03	3.6±0.14	0.22	20.8±2.483	PASS	28.5±4.07	96.28
F7	0.47	0.55	14.54	1.17	28° 81'	2.3±0.05	3.6±0.13	0.25	35±2.097	PASS	33.7±5.31	94.40
F8	0.57	0.68	16	1.19	27° 68'	2.3±0.02	1.5±0.102	0.26	35.7±8.547	PASS	24±7.24	95.00

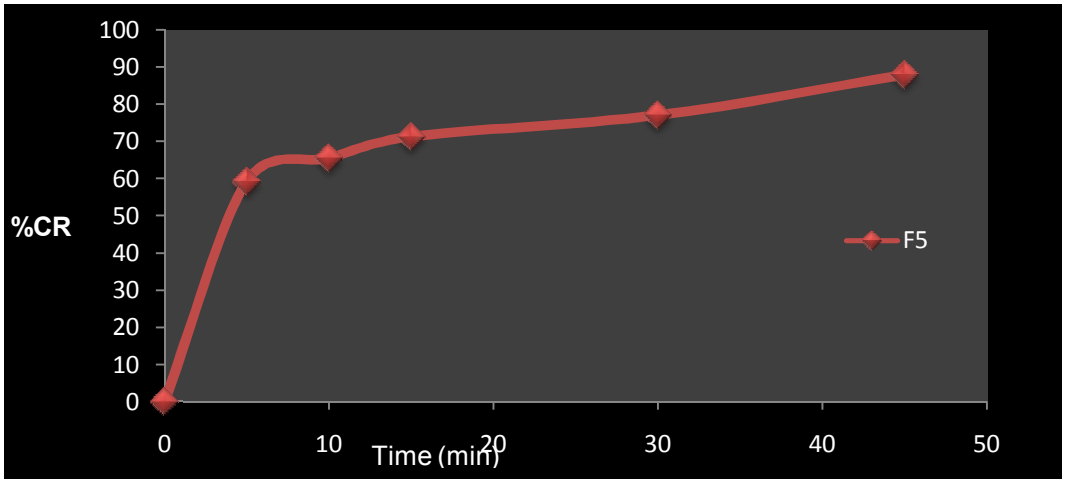

Figure 4: *In-vitro* dissolution profile of F5

RESULT AND DISCUSSION

Results of stability study: Stability study of formulation (F5).

The values of disintegration time, wetting time, hardness, friability of formulations F5 is shown in Table 10.

Table 10. Results of tablet properties of formulations (F5)

Formulation	Disintegration time* (sec)	Wetting time*(sec)	Hardness*(Kg/cm^2)	Friability (%)
F5	9±0.12	8.5±1.70	2±0	0.19

*Average of 6 readings ± SD

Stability study of formulation (f5) after 60 days.

The values of disintegration time, wetting time, hardness, friability of formulations F5 are shown in Table 11.

Table 11. Results of tablet properties of formulations (F5)

Formulation	Disintegration time*(sec)	Wetting time*(sec)	Hardness*(Kg/cm^2)	Friability (%)
F5	9±0.15	10±0.25	2±0	0.17

*Average of 6 readings ± SD

In-vitro dissolution data of the tablet formulations (F5) are shown in Table 49. *In-vitro* dissolution profiles are represented in Fig 16.

Table 12. *In-vitro* dissolution data of F5.

Time (min)	F5
0	0
5	61.2±0.95
10	75±1.85
15	82.4±1.25
30	84.9±0.53
45	89.7±1.66

* The values represents mean±SD, n = 3

The UV spectrophotometric scan of the clonazepam showed a peak exhibits at 309 nm which was found to be same as that of the reported value. Since the dissolution medium for clonazepam tablets as indicated in USP is degassed water, the calibration curve was made accordingly. The calibration curve was found to be linear over concentration range of 2-10µg/ml with R^2 value 0.999.

The IR spectra of the drug, drug-lactose mixture and drug-crospovidone mixture recorded after keeping the sample for 45 days at 40°C and 75% RH was found to be similar with that recorded initially. This indicates absence of interaction between drug and the propose excipients.

The present work was to formulate Fast disintegration tablets of clonazepam using various techniques. In spray drying technique, the mixture of the drug and PVP K-30 was spray dried with an intention to obtain porous mixture which would aid in quicker disintegration. The parameters of spray drying were optimized by trial and error method. Initially drug lactose mixture was used for spray drying as the quantity of drug per tablet is very small. The effect of individual parameters on the final product was checked in Trial 1, Where the inlet temperature was maintained at 60^0 C and outlet temperature was maintained at 40^0 C. This resulted in the product getting collected in the drying chamber itself. To get the final product with very small amount of residual moisture, the inlet temperature must be as highest possible and the temperature difference as small as possible. This approach was used in Trial 2 -8 where the inlet temperature was increased from 75^0C -125^0C and the difference between inlet temperature and outlet temperature was maintained at 15^0 C. In Trial 1, the collection of product was mainly in the drying chamber. Since a higher aspiration speed results in higher degree of separation in the cyclone, in Trial 2 and Trial 3 the aspiration speed was increased up to 70 but the product obtained did not meet the desired criteria. As we was not able to obtain a free flowing porous powder with the above mentioned trials, Drug - PVP K30 mixture was taken up for spray drying (Trial 13). The parameter as specified in Trial 13 resulted in a non-sticky and free flowing powder and yield obtained was 65 %.

The spray dried mixture of drug - PVP K30 was further formulated into tablets using 2^2 factorial design with crospovidone and micro crystalline cellulose as a variable. Among the various super disintegrants crospovidone has been reported to be more effective in reducing the disintegration time mechanism and hence it was selected for the present work. Micro crystalline cellulose was selected as a diluent as it also contributed the hardness of the tablets. The pre-compression parameters were found to be satisfactory. The tablets exhibited a disintegration time in the range of 81-360 sec and wetting time in the range of 60 – 420 sec *In vitro* dissolution study of formulation F2, (which gave least disintegration time (81±0.04 sec) among the four formulations) gave a cumulative release of 47.2 ± 1.1 after 5 min (Table 31, 32 and Fig-10). Though the *in vitro* dissolution profile of this formulation was found satisfactory, the target disintegration time (less than 10 sec) could not be achieved.

The next approach was to formulate the tablets by direct compression method which is reported to be simple and cost effective. The tablets were prepared using crospovidone as a superdisintegrant, lactose and micro crystalline cellulose as diluents. These formulations were also prepared employing 2^2 factorial design with the concentration of crospovidone and micro crystalline cellulose as variables. The pre-compression parameters were found to be satisfactory. The tablets exhibited a disintegration time in the range of 8.7-35.7 sec and wetting time in the range of 13.0-33.7 sec. *In vitro* dissolution study of formulation of F5, (which gave least disintegration time of 8.7±1.08) showed a cumulative release of 59.2 ± 1.13 after 5 min. This method was found to give a low disintegration time and a good release after 5 min.

In the next approach, we decided to use a spray dried excipient as an alternative to spray drying of drug and excipient, spray dried lactose was selected for this purpose as to evaluate the effect of spray dried lactose, lactose used in the previous trials was replaced by spray dried lactose and tablets were prepared by direct compression using 2^2 factorial design. In the next approach the tablets were formulated by sublimation technique using ammonium bicarbonate as subliming agent[52]. Sublimation technique is reportted to yield porous tablets with low disintegration time and hence this technique was also used in present study.

The tablets were prepared using crospovidone as a superdisintegrant, lactose and micro crystalline cellulose as diluents and ammonium bicarbonate as a subliming agent. A 2^2 factorial design was employed with the concentration of crospovidone and ammonium bicarbonate as variables. The pre-compression parameters were found to be satisfactory. The tablets exhibited a disintegration time in the range of 4-14 sec and wetting time in the range of 9.5-29 sec. The sublimation technique was thus found to be suitable to obtain the target disintegration time (< 10 sec) and a good % cumulative release after 5 min.

The various techniques used for fast disintegration tablets of clonazepam were compared. It was found that the direct compression and sublimation technique were beneficial in obtaining the target (10 sec) disintegration time. In direct compression the use of sprayed dried lactose was found to be better than using lactose as the formulation F10 shown DT of 4±0.5 sec compared to DT of F5 which gave DT of 8.7±1.028.

Formulations which gave target disintegration time of less than 10 sec were selected for stability studies. The report of study indicated that the tablets were found to be stable without any significant change in the disintegration time and *in-vitro* release.

Formulation F13 (prepared by sublimation technique) was compared with conventional marketed product of clonazepam by Sun Pharma. It was found that the formulated fast disintegration tablets of clonazepam gave disintegration time of 4.5±0.9 sec compared to the marketed product, which gave a disintegration time of 53.5±1.29 sec. It was also observed that the formulated fast disintegration tablets showed an increase in % CR of 67.2 ± 1.52 after 5 min compared to the marketed product which was found to be 38±1 respectively.

REFERENCES

1. Biradar SS, Bhagavati ST, Kuppasad IJ. Fast Dissolving Drug Deliver Systems: A Brief Overview. The Internet Journal of Pharmacology. 2006 4(2) 26-30.
2. Watanabe Y, Ishikawa Y, Utoguchi N, Matsumoto M. Preparation and evaluation of tablets rapidly disintegrating in saliva containing bitter taste masked granules by the compression method. Chem. Pharm. Bull. 1999; 47: 1451- 1457.
3. Prajapati BG, Nayan R. A Review on Recent patents on Fast Dissolving Drug Delivery System. International Journal of PharmTech Research. 2009; 1(3): 790-798,.
4. Guellec CL, Gaudet ML, Breteau M. Improved selectivity for highperformance liquid chromatographic determination of clonazepam in plasma of epileptic patients, J. Chromatogr. B: Biomed. Sci. Appl. 1998; 719: 227–233.
5. Sallustrio BC, Kassapidis C, Morris RG. High-performance liquid chromatography determination of clonazepam in plasma using solidphase extraction. Ther. Drug Monit. 1994; 16: 174–178.
6. Lillsunde P, Seppala T. Simultaneous screening and quantitative analysis of benzodiazepines by dual-channel gas chromatography using electroncapture and nitrogen–phosphorus detection. J Chromatogr. 1990; 533: 97–110.
7. Song D, Zhang S, Kohlhof K. Quantitative determination of clonazepam in plasma by gas chromatography-negative ion chemical ionization mass spectrometry. J. Chromatogr. B: Biomed. Appl. 1996; 686: 199–204.
8. Robertson MD, Drummer OH. High-performance liquid chromatographic procedure for the measurement of nitrobenzodiazepines and their 7-amino metabolites in blood, J. Chromatogr. B: Biomed. Appl. 1995; 667: 179–184.

9. Kratzsch C, Tenberken O, Peters FT, Weber AA, Kraemer T, Maurer HH. Screening, library-assisted identification and validated quantification of 23 benzodiazepines, flumazenil, zaleplone, zolpidem and zopiclone in plasma by liquid chromatography/mass spectrometry with atmospheric pressure chemical ionization. J. Mass Spectrom. 2004; 39: 856–872.
10. Black DA, Clark GD, Haver VM, Garbin JA, Saxon AJ. Analysis of urinary benzodiazepines using solid-phase extraction and gas chromatography– mass spectrometry. J. Anal. Toxicol. 1994; 18: 185–188.
11. Negrusz A, Moore CM, Kern JL, Janicak PG, Strong MJ, Levy NA. Quantitation of clonazepam and its major metabolite 7-aminoclonazepam in hair. J. Anal. Toxicol. 2000; 24: 614–620.
12. Robertson MD, Drummer OH. Postmortem distribution and redistribution of nitrobenzodiazepines in man. J Forensic Sci. 1998; 43: 9–13.
13. Hilakivi-Clarke LA, Wozniak KM, Durcan MJ, Linnoila M. Behavior of streptozotocin-diabetic mice in test of exploration, locomotion, anxiety, depression and aggression. Physiol. Behav. 1990; 48: 429–433.
14. Massol, J, Martin P, Puech AJ. Antidepressant effects of tricyclic antidepressants and selective serotonin-uptake blockers in diabetic rats. Diabetes. 1989; 38: 1161–1164.
15. Sammour OA, Hammad MA, Megrab NA, Zidan AS. Formulation and optimization of mouth dissolve tablets containing rofecoxib solid dispersion. AAPS PharmSciTech 2006; 7(2):1-9.
16. Shivakumar HN, Desai BG, Murthy N, Sharma A. The disintegration and dissolution of nabumetone dispersible tablets. Pharm Tech. 2007; 2: 62-9.