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DEVELOPMENT AND EVALUATION OF SOLID DISPERSION OF TADALAFIL BY FUSION AND SOLVENT EVAPORATION METHOD

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ABSTRACT

Tadalafil, basically is a phosphor- diesterase-5, selective and potent inhibitor. It is recommended in erectile dysfunction. It is also used in arterial hypertension. It is having low aqueous solubility thus it shows poor bioavailability of about 28% by after oral administration. in current study an attempt was made to study Tadalafil SD formulations to enhance its solubility and dissolution, increase in solubility and thus improvement in its bioavailability. Two different methods were used to prepare SD formulations of Tadalafil, fusion method and solvent evaporation method. Preapred SD formulations were evaluated on different parameters. In the FTIR spectra Tadalafil+PVP K30 and Tadalafil+PEG 6000, there was not any significant change in the peaks, it indicates that the compatibility of Tadalafil with PVP K30 and PEG 6000. The bulk densities of the prepared granules was found to be in between 0.414±0.08 to 0.496±0.06. All SD formulations has shown good flow properties. Repose angle values were in between 21.28±0.08-29.66±0.09. SD formulations are capable to improve the solubility profile of Tadalafil. On basis different evaluation parameters, current study concludes, formulation of batch SD4 was the optimum formulation.

KEYWORDS: Tadalafil, SD formulations, solvent evaporation method, fusion method, *in-vitro* release study.

INTRODUCTION

In present scenario, it is most challenging in the pharmaceutical companies that are related to improve the solubility drugs with poor solubility. Drug's poor solubility may be responsible for less bioavailability. Solubility can be increase by the means of different strategies. These are conversion to amorphous forms, micronization, and solid dispersions (SD) by the means of different hydrophilic carriers. SD development is an impressive way for enhancement of solubility and slow dissolution and thus increase in bioavailability.[1] This technique involves incorporation of poor soluble drugs in hydrophilic carrier substances. Drug and carrier substances, s properties play important roles in formation of the SD.[2] The main mechanism that is responsible for the improved solubility is related to conversion of unstable modifications into some more thermodynamically stable or in amorphous form, reduction in the size of particle, and wettability increment. Thus this will lead of improvement in the bioavailability of drugs having poor solubility by the means of SD formulations.[3]

Tadalafil, basically is a phosphor- diesterase-5, selective and potent inhibitor. It is recommended in erectile dysfunction. It is also used in arterial hypertension. It is having low aqueous solubility thus it shows poor bioavailability of about 28% by after oral administration.[41,4]

Because of this Tadalafil is chosen for the development of SD formulations. So, in current study an attempt was made to study Tadalafil SD formulations to enhance its solubility and dissolution, increase in solubility and thus improvement in its bioavailability. Two different methods were used to prepare SD formulations of Tadalafil, fusion method and solvent evaporation method. Preapred SD formulations were evaluated on different parameters.

MATERIALS AND METHODS

Tadalafil was obtained as gift sample from Rakshit Drugs Pvt Ltd, Hyderabad, India. PVP K30, and PEG 6000 were obtained from Merck, India, Ltd, Mumbai, India. Other reagents used were of analytical grade.

Preparation of Tadalafil SD formulations

Fusion Technique[5,6,7]

Steps followed are-

1. Desired amount of Tadalafil, polymers and other ingredients were weighted out accurately.
2. They were taken in a beaker
3. And placed it into water bath for melting at 70^0c.
4. After melting, accurately weighted amount of drug was added in that glass beaker containing PEG

5. Then they were mixed by glass rod to obtain a viscous mass.
6. The mixture was stirred vigorously for uniform mixing and was kept in normal room temperature for 72 hour until a solid mass was formed.
7. Solidified mixture was then triturated in a mortar by the means of pestle.
8. Obtained powder was sieved (40 mesh size).
9. The resulted samples (Solid dispersion) were weighted and transferred in a fresh vial with proper labeling.
10. Finally, the SD formulations stored in a desiccator.

Solvent evaporation method[8,9,10]

Following steps were used-

1. Accurately weighted amount of Tadalafil, polymers and other ingredients were taken in screw capped test tube and dissolved in very less amount of methanol to get transparent solution.
2. Prepared solution of ingredients was kept in room temperature for few days until the solvent was evaporated from the solution.
3. Residues was allowed to solidify and after it solidified mixture was then grinded to convert powder particles in a mortar with the means of pestle
4. The obtained powder was sieved (mesh size 40).
5. Then the resulted solid dispersion formulation were weighted and transferred in fresh vials with proper labeling.
6. Finally all obtained SD formulations were kept in desiccators.

CHARACTERIZATION OF SD

Micromeritic characterization

Angle (θ) of repose

SD formulations were weighed and kept and dropped from the funnel. A cone like structure gets appear. Heap was measured for radius (r in cm), height (h in cm). Following equation was used to get value of θ.[11]

$$\theta = tan^{-1}\frac{h}{r}$$

Bulk density (BD)

It was determined by filling the already weighed granules (M) in a measuring cylinder. Bulk volume (BV) is recorded from it. BD was determined by following equation.[8]

$$BD = \frac{M}{BV}$$

Tapped density (TD)

The granules were filled in a measuring cylinder having known mass (M). After filling the granules were tapped 100 times. The tapped volume (TV), thus measured. TD was measured using below formula.[12]

$$TD = \frac{M}{TV}$$

Carr's index (CI)

CI for the prepared granules was calculated by below formula.[13]

$$CI = \frac{TD - BD}{BD} x100$$

Hausner's ratio (HR)

This also indicate the potential of granules to flow. It was calculated by below formula.[14]

$$HR = \frac{TD}{BD}$$

If it is less than 1.25, means good flow, but if its value is more than 1.25 it means poor flow of any system.

Solubility estimation

Solubility of Tadalafil and SD formulations of Tadalafil was determined in triplicate using saturation solubility method. Excess amount of SD was mixed in a vial with 10ml buffer (pH 6.8). Content of vials was mixed vigorously for 30 minutes and further solutions were shaken mechanically to equilibrate. After 72 hrs each vial was rotated at 2500 rpm for 10 min in a centrifuge in order to separate the content. Later on it was filtered by the means of 0.45µ pore size membrane filter. Obtained filtrate was diluted with suitable solvent. The concentration of Tadalafil was measured by the means of UV spectrophotometr at 281 nm.[15]

Drug content

SD formulations were tested for estimation of amount of drug content by the means of UV spectrophotometer. SD formulations (equv. To 100mg) were weighed accurately and mixed in a flask with 5ml alcohol. It was mixed properly and diluted to 1oo ml with buffer (6.8 pH). After filterations, dilutions samples checked by UV spectrophotometer at 281nm.[16]

Percentage Yield

In order to determine the efficiency of used method to prepare SD formulations of Tadalafil, the yield was calculated. It was calculated on the basis of used amount of Tadalafil and PVP K30, PEG 6000 and other used ingredients and the final weight of the obtained product.[17]

$$\text{Percentage yield} = \frac{\text{Actual weight of products}}{\text{Weight of drug and excipients}} x100$$

***In vitro* dissolution study**

USP (type II appar.) was used for this study. Paddle speed kept 75rpm and buffer temperature (900 ml, pH 6.8) was kept 37°C. SD formulations (500 mg equivalent wt of drug) were used 5ml sample were taken at regular interval and replaced 5ml buffer solution. Samples were checked through UV spectrophotometer at 281nm.[18]

Accelerated stability study

Based on different evaluation parameters SD formulation of Tadalafil of two batches SD4 and SD8 were found to be optimum formulations. These two formulations were

subjected to accelerated study for the three months at different temperatures. The formulations of two batches SD4 and SD8 were air tight packed and kept for three months on 40°C and 75% RH. The samples were observed by UV spectrophotometer at 281nm for the absorbance. By the means of the calibration curve the amount of the Tadalafil was estimated.[19,20]

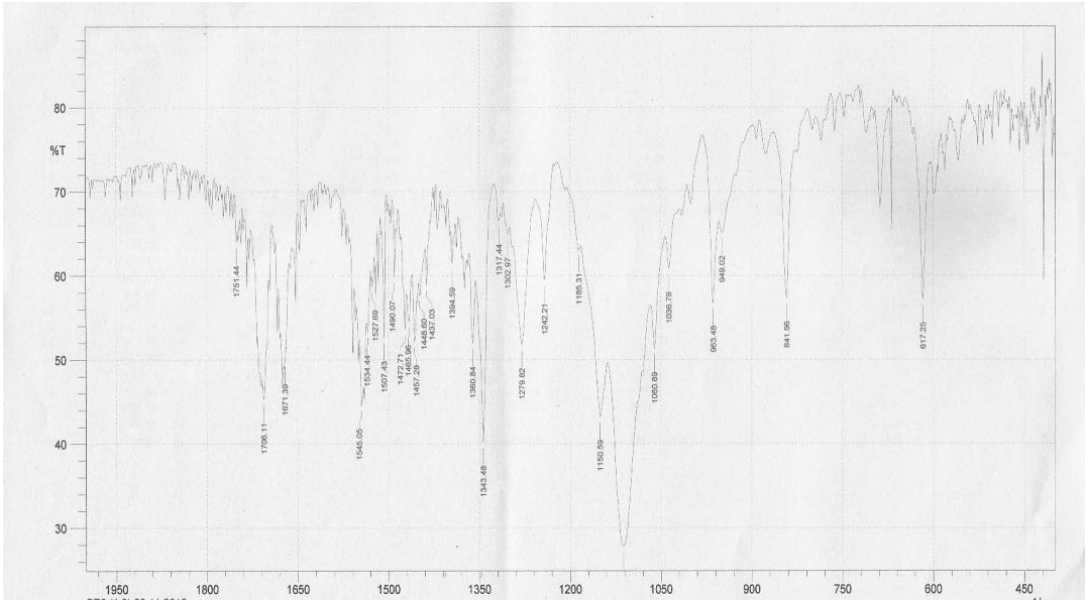

Figure 1: FTIR spectra of mixture of Tadalafil, PVP K30 and PEG6000.

Table 1: SD formulations composition.

S. No.	Formulation code	PVP K30	β cyclodextrin (mg)	PEG 6000 (mg)	Method
1	SD1	400	100	-	Solvent evaporation method
2	SD2	300	200	-	Solvent evaporation method
3	SD3	200	300	-	Fusion method
4	SD4	100	400	-	Fusion method
5	SD5	100	-	100	Fusion method
6	SD6	200	-	200	Fusion method
7	SD7	300	-	300	Solvent evaporation method
8	SD8	400	-	400	Solvent evaporation method
9	SD9	-	400	100	Solvent evaporation method
10	SD10	-	300	200	Solvent evaporation method
11	SD11	-	200	300	Fusion method
12	SD12	-	100	400	Fusion method

Table 2: Micromeritic properties of Tadalafil SD formulations.

Batch	BD* (g/cm^2)	TD* (g/cm^2)	θ*	CR* (%)	HR*
SD1	.461±0.09	.501±0.09	23.65±.19	6.98±0.36	1.086
SD2	0.473±0.11	0.513±0.11	24.73±0.09	7.79±0.28	1.084
SD3	0.432±0.08	0.477±0.07	23.58±0.04	9.43±0.19	1.104
SD4	0.485±0.21	0.525±0.05	25.32±0.11	7.61±0.09	1.082
SD5	0.457±0.08	0.497±0.13	27.48±0.14	8.04±0.13	1.087
SD6	0.466±0.13	0.506±0.08	24.51±0.42	7.90±0.09	1.085
SD7	0.496±0.06	0.532±0.09	21.28±0.08	6.76±0.08	1.072
SD8	0.488±0.03	0.518±0.08	26.73±0.06	5.79±0.12	1.222
SD9	0.414±0.08	0.454±0.13	28.59±0.15	8.81±0.08	1.096
SD10	0.473±0.08	0.523±0.08	29.66±0.09	9.56±0.09	1.103
SD11	0.492±0.09	0.532±0.04	20.45±0.38	7.51±0.12	1.081
SD12	0.436±0.13	0.476±0.03	28.37±0.58	8.40±0.23	1.091

θ- Angle of repose, BD- Bulk density, CR- Carr's compressibility index, TD- Tapped density, HR- Hausner's ratio, n = 3

Table 3: Properties of different SD formulations of Tadalafil.

Batch code	Solubility (mg/ml)*	% Content*	% Yield*
SD1	.205±.93	97.11±0.09	88.73±0.43
SD2	0.213±1.09	99.31±0.11	83.46±0.55
SD3	0.212±0.77	99.57±0.02	90.96±0.67
SD4	0.208±0.62	99.48±0.08	96.32±0.08
SD5	0.207±0.09	98.53±0.13	93.52±0.12
SD6	0.205±0.31	97.62±0.24	92.73±0.21
SD7	0.198±0.42	99.25±0.41	95.48±0.31
SD8	0.197±0.51	98.38±0.52	97.32±0.41
SD9	0.188±0.08	97.43±0.11	98.62±0.18
SD10	0.196±0.11	98.59±0.09	96.49±0.09
SD11	0.188±0.22	98.47±0.06	94.53±0.21
SD12	0.187±0.09	97.58±0.12	89.62±0.18

Solubility of pure drug= 0.128mg/ml. ***** n = 3

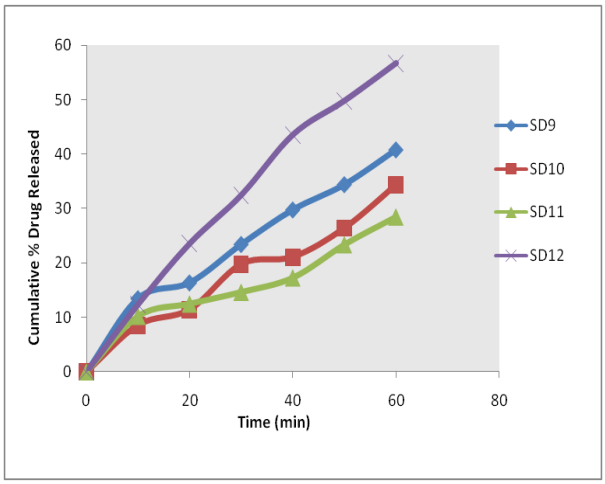

Figure 4: Table 10: *In vitro* disso profile of Tadalafil SD formulations (SD9-SD12).

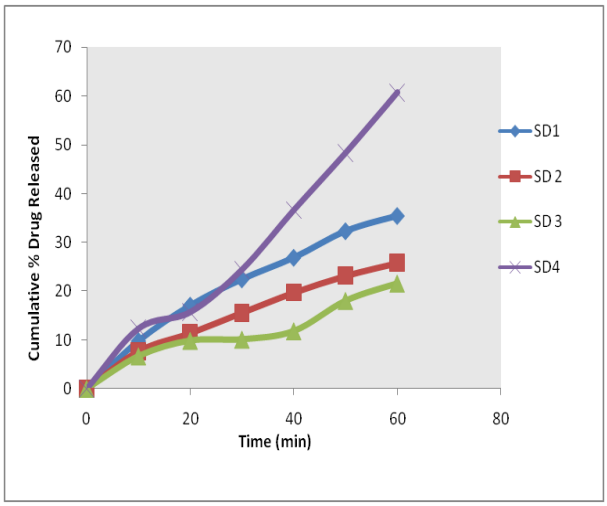

Figure 2*: In vitro* disso profile of Tadalafil SD formulations (SD1-SD4).

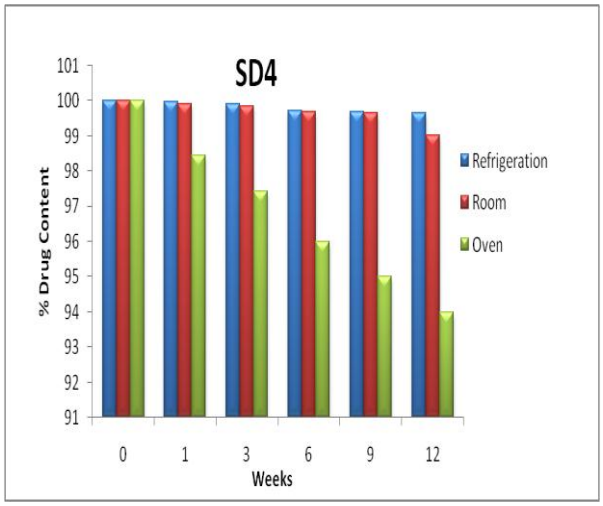

Figure 5: Stability studies of Tadalafil SD formulations of batch SD4 at different temperature.

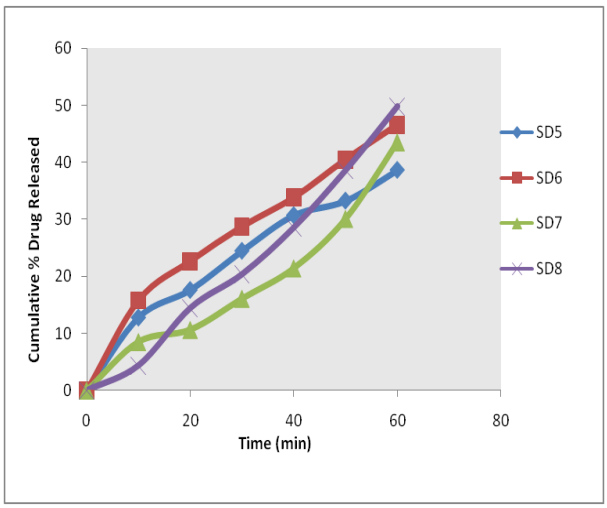

Figure 3: *In vitro* disso profile of Tadalafil SD formulations (batch SD5-SD8).

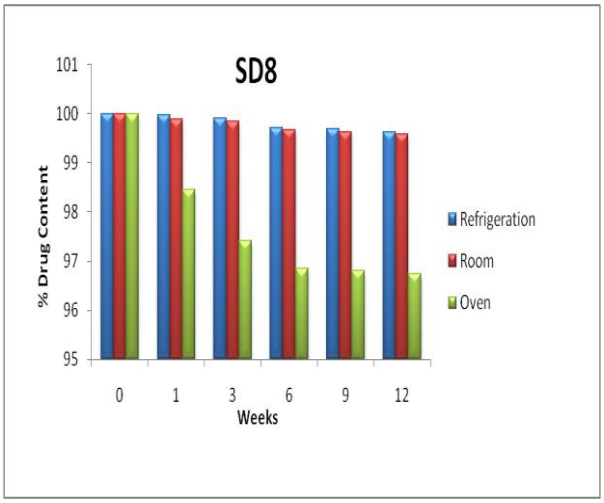

Figure 6: Stability studies of Tadalafil SD formulations of batch SD8 at different temperature.

DISCUSSION

Twelve Tadalafil SD formulations were developed by incorporating different ingredients i.e. PVP K30, β

cyclodextrin, PEG 6000 in different ratio by Fusion method and Solvent evaporation method.

6.4: Micromeritic properties of SD formulations

The bulk densities of the prepared granules was found to be in between 0.414±0.08 to 0.496±0.06 (Table 6 and Table 7). Low densities leads to increase in porosity and thus improved capacity of packing. The tapped densities of the prepared granules was found to be in between 0.454±0.13–0.532±0.04 g/cm^3. All SD formulations has shown good flow properties. Repose angle values were in between 21.28±0.08-29.66±0.09. These values are in between 20 to 40, indicates good flow properties and they are non-aggregated. Carr's index for all SD formulations were in between. 79±0.12 to 9.56±0.09 %. These values indicate, excellent compressibility. So, they having good packabilty while filling in capsule. Hausner's Ratio values for all twelve formulations were in the range of 1.072–1.266. As the amount were <1.25, means good flow was there.[21]

6.65: Drug content and percentage yield

% drug content in developed 12 SD formulations of Tadalafil was found to be in between 97.11±0.05 to 99.57±0.02 indicating good amount of drug in all formulations. This indicate very less waste of the drug during manufacture of the formulations.

The percentage yield of the floating beads was between 83.46±0.55 to 98.62±0.18 %.

6.6: Solubility of the formulations

Result of saturation solubility study revealed that there was increase in solubility. In current study drug has shown solubility of 0.128mg/ml, while formulations has shown solubility range in between 0.187±0.09 to 0.213±0.51. Maximum solubility was shown by the SD formulations of batch SD2 having PVP K30. It revealed remarkable decrease in crystallinity of Tadalafil in molecular dispersion form with PVP-K30. Those formulations that were developed by fusion method has shown more solubility in comparison to those prepared by another method of solvent evaporation.[22]

6.7: *In vitro* dissolution study

Study reveals that Tadalafil released amount was depending on the used polymers amount. This study indicate that the amount of drug release is affected by the amount of polymers used.[22] In 60 min study, the batch SD4 has shown maximum drug release 60.69±0.09%.

6.8: Stability study

Accelerated stability studies for 12 weeks shows that the selected SD formulations of Tadalafil SD4 and SD8 are capable to be stable at 45^{0}C as well as at refrigeration temperature. Therefore, the SD formulations of Tadalafil may be kept at room temperature without affecting the properties.

CONCLUSION

SD formulations are capable to improve the solubility profile of Tadalafil. On basis different evaluation parameters, current study concludes, formulation of batch SD4 was the optimum formulation.

REFERENCES

1. Chaulang G. Formulation and Evaluation of Solid Dispersions of Furosemide in Sodium Starch Glycolate. T J Pharm Res., 2009; 8(1): 43-51.
2. Magdum SS. Liquisolid technique for dissolution and bioavailability enhancement of poorly soluble drugs. Universal Journal of Pharmaceutical Research, 2017; 2(5): 42-49.
3. Dhilon N, Midha K, Nagpal, Pahwa R. Formulation Optimization and Characterization of solid dispersion of glibenclamide. Pharma Methods, 2015; 6(2): 72-82.
4. Mekonnen T. Design and evaluation of fast dissolving buccal films containing Tadalafil. Int J Allied Medical Sci Clin Res., 2016; 4(2): 155-63.
5. Meka AK, *et al.* Development, evaluation and characterization of surface solid dispersion for solubility and dissolution enhancement of Irbesartan. Int J Drug Dev Res., 2012; 4(1): 263-273.
6. Akiladevi D, *et al.* Preparation and evaluation of paracetamol by solid dispersion technique. Int J Pharm Pharm Sci., 2011; 3(1): 188-191.
7. Park JH, *et al.* Preparation and evaluation of cremophor-free paclitaxel solid dispersion by a supercritical antisolvent process. J Pharm Pharmacol, 2011; 63: 491–499.
8. Kumar N Development, characterization, and solubility study of solid dispersion of terbinafine hydrochloride. Int J Pharm Sci Nanotech, 2008; 1(2): 171-176.
9. Mahmoud A. Younis. Solid dispersion technology, a contemporary overview on a well established technique. Universal Journal of Pharmaceutical Research, 2017; 2(3): 14-18.
10. Agarwal P, Semimul A. A comprehensive review on sustained release matrix tablets: a promising dosage form. Universal Journal of Pharmaceutical Research, 2018; 3(6): 53-58.
11. Jun SW *et al.* Cefuroxime axetil solid dispersions prepared using solution enhanced dispersion by supercritical fluids. J Pharm Pharmacol, 2005; 57: 1529–1537.
12. Al-Nima AM, *et al.* Preparation and Evaluation Of meloxicum solid dispersions by solvent evaporation method. Int Res J Pharm., 2014; 5(11): 833-845.
13. Bikiaris D, George Z. Physicochemical studies on Solid dispersion poorly water soluble drugs, evaluation of capabilities and limitations of thermal analysis technique. Thermochimia Acta, 2005; 439: 58-67.
14. Sukanya M, Kishore VS. Design and Development of solid dispersions of simvastatin for enhancing the solubility. Am. J. Pharm Tech Res., 2012; 2(4): 733-740.

15. Verreck G, *et al.*. Characterisation of solid dispersions of Itraconazole and HPMC prepared by melt extrusion part-I. Int J Pharm Sci., 2003; 251: 165-174.
16. Singh A, *et al.*. Evaluation of enhancement of solubility of paracetamol by solid dispersion technique using different polymers concentration. Asian J Pharm Clin Res., 2011; 4(1): 117-119.
17. Akhter S, Hossen MS, Salahuddin M, Sunny MA, Sathi FA, Islam MS. *In vitro* dissolution study of glimepiride from binary and ternary solid dispersion formulation. Universal Journal of Pharmaceutical Research, 2019; 4(5): 7-11.
18. Mahaparale PR, Gudsoorkar VR, *et al*. Studies on solid dispersions of meloxicam. Ind J Pharm Educ Res., 2006; 40(4): 241- 244.
19. Rao M, Mandage Y, Thanki K, Bhise S. Dissolution improvement of simvastatin by surface solid dispersion technology. Dissolution Tech, 2010; 17(2): 27-34.
20. Jajere UM, Achadu AE. Fabrication and characterization of ezetimibe solid dispersion for solubility enhancement. Universal Journal of Pharmaceutical Research, 2017; 2(1): 11-14.
21. Md. Shahidul Islam, Rasheda Akter Lucky. Development and *in vitro* dissolution study of binary and ternary solid dispersions of aceclofenac. Universal Journal of Pharmaceutical Research, 2019; 4(1): 29-34.
22. Kumar A, Kumar K. Solid dispersion-strategy to enhance solubility and dissolution of poorly water soluble drugs. Universal Journal of Pharmaceutical Research, 2017; 2(5): 50-55.