Multidisciplinary Review Journal

Journal of Critical Reviews

ISSN- 2394-5125 Vol 7, Issue 2, 2020

Review Article

DESIGN AND EVALUATION OF FAST DISSOLVING TABLET CONTAINING TADALAFIL SOLID DISPERSION

[1]MANSI SHAH, [2]DIPTI PATEL

Department of Pharmaceutics, Parul Institute of Pharmacy and Research, Faculty of Pharmacy, Parul University, A/P: Limda, Tal: Waghodiya, Dist. Vadodara, Gujarat, India
Department of Pharmaceutics, Parul Institute of Pharmacy and Research, Faculty of Pharmacy, Parul University, A/P: Limda, Tal: Waghodiya, Dist. Vadodara, Gujarat, India dipti2603@yahoo.com

Received: 05.11.2019 ***Revised: 10.12.2019*** ***Accepted: 11.01.2020***

Abstract
Fast dissolving tablet containing tadalafil solid dispersion was developed to improve the dissolution of drug. In the present work, fast dissolving tablets of tadalafil were prepared by direct compression. Fast dissolving tablet increase the patient compliance. Solid dispersion prepared by spray drying method. Three super-disintegrants, viz., crospovidone, croscarmellose sodium and sodium starch glycolate in different ratios with microcrystalline cellulose PH-102 along with directly compressible mannitol to enhance mouth feel. All formulations were evaluated for physical characteristics of compressed tablets such as weight variation, hardness, friability, content uniformity, in vitro disintegration time, wetting time and in vitro dissolution study. Among all, the formulation T2 containing 4% w/w concentration of crospovidone was considered to be the best formulation with Drug content 99.25%, disintegration time of 22 sec, wetting time of 35 sec and in vitro drug release of 99.73% in 30 min and 83.36 in 15min.

Keywords: Tadalafil, Fast dissolving tablets, Crospovidone, croscarmellose sodium, sodium starch glycollate

DOI: http://dx.doi.org/10.31838/jcr.07.02.106

INTRODUCTION

Tadalafil is a potent and selective cyclic guanosine monophosphate specific type (V) phosphodiesterase inhibitor. Erectile dysfunction, pulmonary arterial hypertension and benign prostatic hyperplasia can be cured using tadalafil. [1, 2] Tadalafil is a first-line therapy in the treatment of erectile dysfunction (ED). Longer duration of action of Tadalafil is approximately 36 h which is the most advantageous characteristic in comparison with other drugs in pharmacology. Tadalafil belongs to biopharmaceutical classification system class II; Low aqueous solubility and dissolution of drug manifests low *in-vivo* bioavailability. To enhance solubility, dissolution and bioavailability of poorly water soluble drugs different approaches like size reduction, complexation, formation of solid dispersions and the surfactants are used[3, 4]. Solid dispersions are one of the most promising approaches to the solubility improvement of poorly soluble drug substances which represent the vast majority of currently investigated drugs. When solid dispersions is introduced to an aqueous environment, the carrier dissolves leaving the drug as fine colloidal particles. This idea has number of advantages like no use of toxic constituents, a simple process and flexibility. One of the most extensively studied dissolution enhancing approach is formation of solid dispersions. Many techniques are used to make a solid dispersion. Spray drying is widely used in pharmaceutical processing because it requires only a one-step process and can be easily controlled and scaled up [5]. Tablets are the most extensively used dosage form because of its ease in terms of self-administration, compactness, and convenience in manufacturing. Large number of patients expresses difficulty in swallowing tablets and hard gelatin capsules, resulting in noncompliance and ineffective therapy [6]. To get rid of this loophole, scientists have formulated creative drug delivery systems called fast dissolving tablets. Solid dosage forms that can be disintegrated, dissolved, or suspended by saliva in the mouth results in easy swallowing and can provide significant benefits to the pediatric and geriatric populations, as well as other patients who prefer the convenience of easily swallowable dosage forms.

The goal of this study was to formulate fast dissolving tablet of tadalafil solid dispersion to improve the solubility and dissolution profile with the help of skimmed milk as a solid dispersion. The skimmed milk is a colloidal suspension of casein micelles, globular proteins and lipoprotein particles [7]. Formulated directly compressible fast dissolving tablets of tadalafil has sufficient mechanical integrity, content uniformity and acceptable palatability to assist patient's compliance and good mouth feel.

Preparation of Solid dispersion

A solid dispersion containing tadalafil with skimmed milk powder in ratio of 1:10 was prepared by spray drying method. The drug and carrier were prepared according to the specified drug-to-carrier ratio. Tadalafil was dissolved in ethanol and the carrier was dissolved in water. Sonicate the solution for 15 minutes. The solution was spray dried in a labultima spray drier at inlet temperature of 140 °C, outlet temperature of 90°C and flow rate of 5ml/min. The obtained free flowing powder was stored in well tight container for further use.

Saturation solubility studies

Equivalent amount of tadalafil and solid dispersion formulations containing the drug were placed in a flask with glass stopper containing water. The samples were placed on a shaker for 48 h at 37±0.5°C until equilibrium was achieved. The aliquots were filtered through 0.45 µm nylon membrane filter. The samples were diluted appropriately. Final sample was assayed using a UV-visible spectrophotometer against a blank solution at 284 nm.

Preparation of fast dissolving tablets

Table 1 below shows the formula of fast dissolving tablets of tadalafil. All the ingredients except glidants and lubricant were passed through # 40 mesh separately and then glidants and

lubricant passed through # 65 mesh. Then the ingredients were weighed and mixed in geometrical order and compressed into tablets of 300 mg using 12 mm round flat punches on 12 station rotary tablet machine. A batch of 50 tablets was prepared for each of the designed formulations.

Table 1: Formulation of Fast dissolving tablet

Sr. No.	Ingredients	Quantity (mg)								
		T1	T2	T3	T4	T5	T6	T7	T8	T9
1	Tadalafil	110	110	110	110	110	110	110	110	110
2	MCC pH 102	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
3	PVP K-30	15	15	15	15	15	15	15	15	15
4	Mannitol	24	24	24	24	24	24	24	24	24
5	Crosspovidone	12	18	24	-	-	-	-	-	-
6	Cross carmelose sodium	-	-	-	12	18	24	-	-	-
7	Sodium starch glycolate	-	-	-	-	-	-	12	18	24
8	Vanilla flavor	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5
9	Talc	3	3	3	3	3	3	3	3	3
10	Magnesium stearate	3	3	3	3	3	3	3	3	3
	Avg Weight	**300 mg**								

Evaluation of tablet characteristic

Prepared tablets were studied for hardness, friability, wetting time, *drug* content, *in-vitro* disintegration time and *in-vitro* dissolution study. For determination of tablet hardness, monsanto hardness tester was used. The crushing strength limit of the tablets was in the range of 3-5 kg/cm^2. Roche friabilator was used to evaluate the friability of the tablets. Rotation of ten pre-weighed tablets was performed for 4 min at 25 rpm. After 100 rotations the tablets were weighed, and the calculation of the percentage weight loss was performed. The limit of the percent friability was less than 1%. Tablet disintegration apparatus was used to perform *in-vitro* disintegration test on six tablets in distilled water at 37°C ± 2°C. The time taken for complete disintegration of the tablet with no noticeable mass remaining in the apparatus was measured in seconds. In order to evaluate the wetting time, a piece of tissue paper folded twice was kept in a small petridish having 5 ml of water. The tablet was now placed on the paper to measure the wetting time.

To determine the drug content, randomly tablets were selected and pulverized to fine powder. The weight equivalents to 10 mg of tadalafil were dissolved separately in 10 mL of Water and shaken for 10 min. Now, add 30ml methanol, sonicate it for 10 min and make the volume with the 0.5% sodium lauryl sulfate [13]. The solution was filtered and further diluted so that the absorbance fell within the range of standard curve. The samples were filtered through a 0.45 µm membrane filter and the drug content was determined spectrophotometrically at 284 nm. The blank formulation was treated in the same manner as the tadalafil formulations to minimize the interference of protein in the skimmed milk. The results are shown in table 2 and disintegration time shown in Fig 1.

Table 2: Evaluation of tablet

Batch No	Hardness (IP) Kg/cm^2	Friability (%)	Weight variation % deviation	Wetting time (sec) ± SD	Disintegration time (sec) ± SD	Drug Content (%) ± SD
T1	3.3±0.05	0.44	+1%	35±1.15	26±1.52	98.56±1.15
T2	3.1±0.05	0.50	-2.1%	32±1.00	22±1.52	99.25±0.42
T3	3.0±0.10	0.55	+1.2%	37±1.15	30±2.00	97.25±0.93
T4	3.1±0.11	0.49	+0.5%	46±1.52	38±1.00	96.78±0.51
T5	2.9±0.15	0.55	+0.8%	47±1.52	36±1.52	98.15±0.28
T6	3.0±0.10	0.52	-1.3%	43±2.00	30±2.00	100.32±0.63
T7	2.9±0.05	0.68	+2.1%	81±2.00	60±1.52	97.38±0.33
T8	2.9±0.15	0.65	+0.3%	80±1.52	64±1.00	97.25±0.46
T9	2.8±0.10	0.72	+1.5%	83±2.00	69±1.52	99.32±0.75

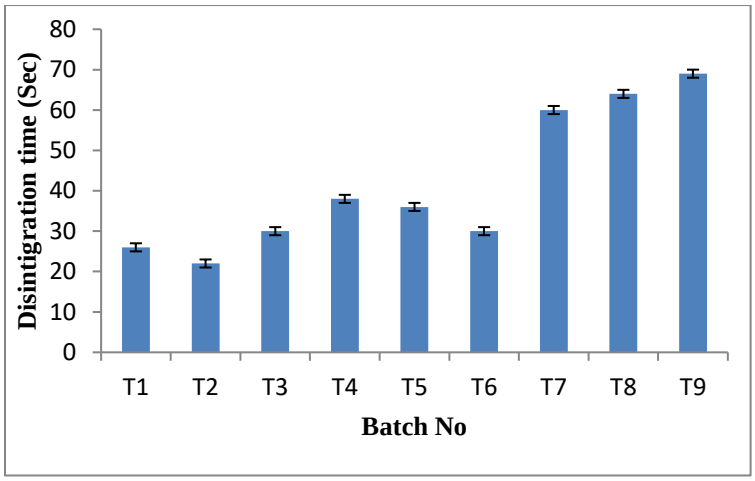

Fig. 1: Disintegration time of T1 –T9 formulation

USP Apparatus 2 was used to perform *in-vitro* dissolution study of fast dissolving tablets. 1000 ml of 0.5% sodium lauryl sulfate was used to carry out the dissolution test. The temperature maintained was 37°C ± 0.5°C and rotation of apparatus was 50 rpm. At specific time intervals a sample of the solution was withdrawn from the dissolution apparatus and withdrawn volume was replaced with fresh dissolution media, filtered and calculated spectrophotometrically. The results are shown in table 3 and Fig. 2.

Table 3: *In vitro* Dissolution of T1 –T9 formulation

Batch No	Dissolution in 0.5% SLS Time (min)					
	5	10	15	20	25	30
T1	28.25±0.72	58.55±0.94	79.54±1.27	90.68±1.34	95.69±1.09	98.65±1.25
T2	30.75±0.81	63.45±1.66	85.36±0.67	97.21±1.46	99.25±1.55	99.73±1.43
T3	23.65±0.63	51.26±0.80	71.79±0.98	91.28±1.08	96.46±0.96	98.44±1.25
T4	20.19±0.59	44.25±0.56	69.65±1.01	90.48±0.67	93.15±0.86	97.26±0.68
T5	25.36±0.53	49.46±0.88	74.27±1.56	92.48±1.46	98.44±1.13	98.49±0.69
T6	26.54±0.41	53.36±1.09	79.84±0.94	95.22±0.66	98.57±1.09	98.36±1.07
T7	20.27±0.92	43.45±1.36	66.85±1.36	86.59±0.88	91.85±0.91	97.54±1.01
T8	23.21±0.81	45.86±0.72	69.54±0.91	81.46±1.20	90.15±0.55	95.56±1.51
T9	18.26±0.87	40.84±1.70	63.18±0.98	81.56±1.44	91.78±0.77	97.25±1.15

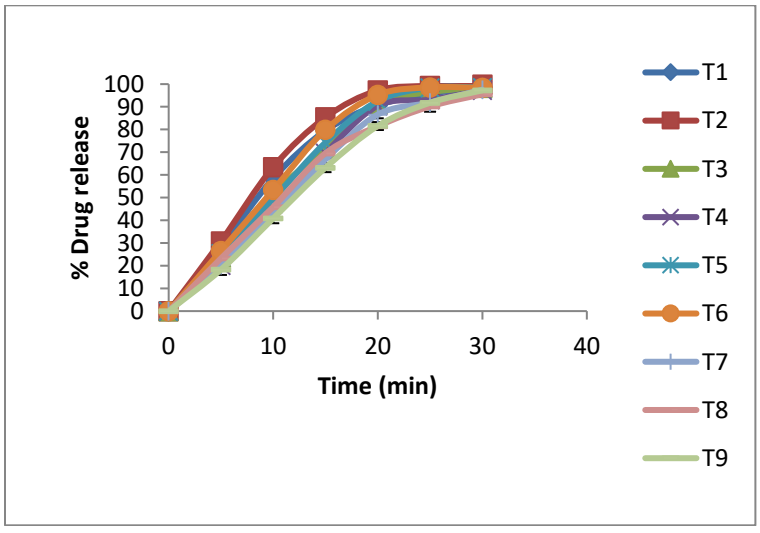

Fig. 2: In vitro Dissolution of T1 –T9 formulation

RESULTS:

The present development was taken to evaluate tadalafil solid dispersion fast dissolving tablet. Water solubility of pure tadalafil tablet was found to be 0.0023±0.0004 mg/ml and solid dispersion solubility was found to be 0.0719±0.004 mg/ml. Hardness of the tablet was found to be in the range of 2.8-3.3 kg/cm^2. All the formulated tablets passed weight variation test as the % weight variation was within the IP limits of ± 5% of the weight. The friability of all batches (T1-T9) was found to in the range of 0.44 – 0.72 %. Wetting time of all formulation was in the range of 32-82 sec. Disintegration time was in range of 22-69 sec. Drug content of all formulation was found in the range of 97-100%. *In-vitro* dissolution at different time interval is shown in table 3 and Fig.2. All formulation showed drug release around 90-99 %. Formulation with 4% crospovidone superdisintegrants showed drug released around 99 % in 30 min and in 15 min it showed dug release 85.36 %.

DISCUSSION:

Fast dissolving tablet of this tadalafil solid dispersion was prepared successfully. Solid dispersion of tadalafil with skimmed milk increases the solubility. Significant change in solubility was around 30 fold[14]. Superdisintegrants at concentration of 2, 4, 6 % w/w used to formulate tablet. All tablets were white, odorless and flat in shape with smooth surface. All the formulated tablets passed weight variation test. Friability was satisfactory of the fast dissolving tablet. This indicates tablets with lower range of friability may not break during handling or shipping. Wetting time and *in-vitro* disintegration time is prime evaluation parameter for fast dissolving tablet. *In-vitro* disintegration time was excellent (lowest) when crosspovidone used as a disintegrant, whereas sodium starch glycolate shown poor (highest) disinitration time. The rapid disintegration may be due to the rapid intake of water from the medium, swelling and burst effect. Sodium starch glycolate showed more gelling effect which extended the disintegration time. All the formulation showed good *in-vitro* drug release, but T2 batch showed the results which was desired.

CONCLUSION

Formulation with 4% crospovidone superdisintegrants showed better drug release which is highest amongst all the formulation. From the overall observations, formulation T2 containing 4% w/w Crospovidone was considered to be the best formulation. The effectiveness of superdisintegrants was in the order of Crospovidone > croscarmellose sodium > Sodium starch glycollate.

ACKNOWLEDGEMENTS

The authors thank Parul institute of pharmacy and research, parul univerity, Vadodara, for providing required facilities to carry out this research work.

CONFLICT OF INTEREST – The authors declare that there are no conflicts of interest.

REFERENCES

1. Arif, S.A., & Poon, H. (2011). Tadalafil: a long-acting phosphodiesterase-5 inhibitor for the treatment of pulmonary arterial hypertension. Clin. Ther, 33, 993–4.
2. Mcvary, K.T., Roehrborn, C.G., Kaminetsky, J.C., Averbach, S.M., Wachs, B., Young, J.M., Esler, A., Sides, G.D., & Denes, B.S.(2007). Tadalafil relieves lower urinary tract symptoms secondary to benign prostatic hyperplasia. J. Urol, 177, 1401–7.
3. Vasconcelos, T., Sarmento, B., & Costa, P. (2007). Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs. Drug Discov Today, 12, 1068–75.
4. Kawabata, Y., Wada, K., Nakatani, M., Yamada, S., & Onoue, S. (2011). Formulation design for poorly water-soluble drugs based on biopharmaceutics classification system: basic approaches and practical applications. Int. J. Pharm, 420, 1–10.
5. Moretti, M.D., Gavini, E., Juliano, C., Pirisino, G., & Giunchedi, P. (2001). Spray-dried microspheres containing ketoprofen formulated into capsules and tablets. J Microencapsul, 18(1), 111-21.
6. Seager, H. (1998). Drug delivery products and the Zydis fast dissolving dosage forms. J Pharm Pharmacol, 50, 375–82.
7. Sahin, NO., & Arslan, H. (2007). Inclusion complex of prednisolone with skimmed milk. Part I: physicochemical characterization. 127(8), 1255-1261.
8. Wlodarski, K., Tajber, L., & Sawicki, W. (2016). Physicochemical properties of direct compression tablets with spray dried and ball milled solid dispersions of tadalafil in PVP-VA. Eur J Pharm Biopharm, 109, 14–23.
9. Aslı Zungur, B., Dilara, T., Mehmet, K., & Figen Kaymak, E. (2016). Spray dried melon seed milk powder: physical, rheological and sensory Properties, J Food Sci Technol, 53(5), 2396–04.
10. Lu, M., Xing, H., Yang, Z., & Ding, P. (2016). Dissolution enhancement of tadalafil by liquisolid technique. Pharma Dev Tech, 10(5), 1-13.
11. Shirsand, S., suresh, S., Swamy, P., Nagendra, D., & Rampure, M. (2008). Design and evaluation of fast dissolving tablets of clonazepam. Indian J. Pharm. Sci, 70(6), 791- 95.
12. Lachman. L., Lieberman, A., Kinig, J.L. (1991). Bombay: Varghese Publishing House; 1991. The Theory and Practice of Industrial Pharmacy; pp. 67–8. (4th ed)
13. Wlodarski, K., Sawicki, W., Paluch, K.J., Tajber, L., Grembecka, M., Hawelek, L., Wojnarowska, Z., Grzybowska, K., Talik, E., & Paluch, M. (2014). The influence of amorphization methods on the apparent solubility and dissolution rate of tadalafil. Eur. J. Pharm. Sci, 62, 132–40.
14. Ankush, C.,Avtar C.R.,Geeta, A.,Virender, K.,Foziyah, Z. (2016). Development and characterization of an atorvastatin solid dispersion formulation using skimmed milk for improved oral bioavailability. Acta pharma sinica B, 4(2), 421-28.
15. Susi Ari Kristina, Yosef Wijoyo. "Assessment of Pharmacy Students' Clinical Skills using Objective Structured Clinical Examination (OSCE): A Literature Review." Systematic Reviews in Pharmacy 10.1 (2019), 55-60. Print. doi:10.5530/srp.2019.1.9