Research Article

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Insights in Analytical Electrochemistry

2020
Volume: 6 Issue: 3 : 4

DOI: 10.21767/2470-9867.100104

Challenges of using HPLC analysis in dissolution testing of Flash tablets (ODT) Technology

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Citation: Bahlai; Challenges of using HPLC analysis in dissolution testing of Flash tablets (ODT) Technology; 2020; 6(3)

Received: April 13, 2020; **Accepted: :** April 20, 2020; **Published:** May 04, 2020

Introduction

There are many patients for whom traditional tablets and capsules are not ideal dosage forms. It is difficult to persuade infants and very young children to swallow them, and they may pose a choking hazard. Older children may simply not want to take them. Adults can have difficulties, too, for example bariatric or geriatric patients often find swallowing a challenge, and those who have Parkinson's disease can be particularly badly affected.

Flash tablets or Orally disintegrating tablets (ODTs) provide an alternative to overcome these challenges. They resemble a traditional tablet but have one important difference: they disintegrate rapidly in the mouth, and therefore do not need to be swallowed. As well as the patient groups identified above, a significant proportion of the general population finds swallowing tablets difficult, and an ODT can greatly increase compliance. No liquid is required when taking the medication either, which is a significant advantage when on the go. ODTs have remarkable disintegration properties: They disintegrate rapidly, usually within a matter of seconds, when placed upon the tongue and can be swallowed without water or chewing (3). ODTs offer ease of administration and improved compliance, particularly in certain populations such as paediatric, elderly, and patients with swallowing difficulties. ODTs are also useful for those who have little or no access to water, such as travellers. The rapid onset of action is of benefit in drugs designed to treat acute conditions, such as migraines and psychiatric incidents, as well as conditions like insomnia. Furthermore, if the drug is absorbed within the oral cavity rather than being digested, it avoids the first pass of the liver. This pre-gastric absorption can reduce side effects caused by metabolites formed by liver enzymes. However, ODT technology experience serious challenges in the form of bad taste. Therefore, taste masking is key for the success of such technology. Hence one of the main applications of ODT is taste masking of active Pharmaceutical ingredients.

The present study purpose is to evaluate orally disintegrating tablets using HPLC Methodology and dissolution profiles for such platform dosage form which presents a challenge for analytical analysis and for HPLC testing.

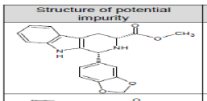
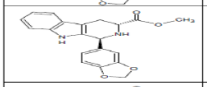
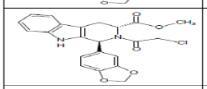
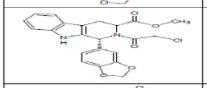
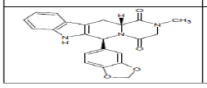
The author has taken a real example of Tadalafil formulation as ODT and doing the dissolution profile and using HPLC analysis.

Tadalafil is a potent and selective inhibitor of phosphodiesterase type 5 (PDE5), the enzyme responsible for the degradation of cyclic guanosine monophosphate (cGMP). Pulmonary arterial hypertension is associated with the impaired release of nitric oxide by the vascular endothelium and consequent reduction of cGMP concentrations within the pulmonary vascular smooth muscle. PDE5 is the predominant phosphodiesterase in the pulmonary vasculature. Inhibition of PDE5 by tadalafil increases the concentrations of cGMP resulting in relaxation of the pulmonary vascular smooth muscle cell and vasodilation of the pulmonary vascular bed. The chemical name of tadalafil is (6R-trans)-6-(1,3benzodioxol-5-yl)-2,3,6,7,12,12 a-hexahydro-2-methylpyrazino [1',2':1,6] pyrido [3,4-b] indole-1,4-dione. It is official in the European Pharmacopoeia.

The below study was to the development and validation of a new HPLC method for tadalafil impurities and degradation products in the ODT formulation using method developed internally in Inova analytical laboratory, which is described under below under method.

Below are the impurities profile of Tadalafil API which was used in the current studies.

Table-1

Structure of potential impurity	Symbol	Previous name	Current name
	TF-3C	(1R,3R)-1-(1,3-benzodioxol-5-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid methyl ester	(1R,3R)-1-(1,3-Benzodioxol-5-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylic acid methyl ester
	TF-3T	(1S,3R)-1-(1,3-benzodioxol-5-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid methyl ester	(1S,3R)-1-(1,3-Benzodioxol-5-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylic acid methyl ester
	TF-4T	(1S,3R)-1-(1,3-benzodioxol-5-yl)-2-(chloroacetyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid methyl ester	(1S,3R)-1-(1,3-Benzodioxol-5-yl)-2-(chloroacetyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylic acid methyl ester
	TF-4C	(1R,3R)-1-(1,3-benzodioxol-5-yl)-2-(chloroacetyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid methyl ester	(1R,3R)-1-(1,3-Benzodioxol-5-yl)-2-(chloroacetyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylic acid methyl ester
	TF-Z	(6S,12aR)-6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methylpirazine-[1',2':1,6]pyrido[3,4-b]indole-1,4-dione	(6S,12aR)-6-(1,3-Benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methylpyrazino[1',2':1,6]pyrido[3,4-*b*]indole-1,4-dione

Materials and methods

Tadalafil was purchased from Polpharma Pharmaceutical Co., Ltd. (Poland). Hydroxypropylmethylcellulose (HPMC–Pharmacoat® 603, viscosity grade is 3 cP) was a gift from Shin-Etsu Chemical Co., Ltd (Tokyo, Japan). Eudragit was a gift from Degussa Chemicals Co., Ltd (Germany). Low-substituted hydroxypropylcellulose was a gift from JRS (Germany). Crospovidone XL was a gift from ISP Technologies, Inc. (U.S.A.). Croscarmellose sodium and microcrystalline cellulose PH101, 102 and Sodium starch glycolate was a gift from JRS (Germany). Spray-dried mannitol was a gift from Roquette. Acetonitrile, n-Hexane, and 2-Propanol from Merck (Darmstadt, Germany) and all chemicals were analytical grade. Water used was purified by a Milli-Q Academic water purification system (Millipore, Eschborn, Germany).

Tadalafil standard and impurities were sourced from Polpharma (Poland).

Chromatographic Parameters

Waters HPLC system consisting of a high-pressure pump with an online degasser, an autosampler, a column oven, and a variable wavelength detector was used for all experiments. A diode array detector from Waters was used for determining spectral peak purity. Column • Waters, XBridge, C18, (50 X 4.6) mm 3.5g, or Equivalent. Flow Rate: 1.0 mL/min Wavelength • 230 nm. Column Temperature 40C. • Sample Temperature: 20C. Injection volume:10 µL.

Mobile Phase

Prepare a filtered and degassed mixture of 0.1% Aqueous Orthophosphoric acid and Methanol (55:45). 0.1% Aqueous Orthophosphoric acid: Dilute 1 ml of 85% Orthophosphoric acid in 1000ml Water. Methanol was used as Diluent.

Standard Preparation

Weigh accurately 20.0 mg ± 5% of Tadalafil working standard into a 100 ml of volumetric flask, add 50 ml of Methanol, sonicate for 5 minutes. Dissolve and complete to volume with Methanol. Take 5 ml of this solution to 20 ml volumetric flask, complete to volume with Methanol and mix. Filter through 0.45 pm PTFE filter.

Sample preparation

Weigh and finely powder not fewer than 20 tablets. Transfer an accurately weighed portion of powder equivalent to 20mg of Tadalafil to 100 ml volumetric flask, add about 50 ml of Methanol, sonicate for 30 minutes, allow cooling down to room temperature. Complete to volume with Methanol. Centrifuge at 3000 rpm for 10 min., Dilute 5 ml of the supernatant into 20 ml of Methanol and mix. Filter through 0.45 PTFE filter.

Dissolution Study profile

Dissolution study was performed by placing the ODT tablet equivalent to 20 mg of Tadalafil in 1,000 ml purified water (and other medias), using the paddle method at 50 rpm and 37 ± 0.5°C. Dissolution medium (5 ml) was withdrawn at specified time intervals and centrifuge the sample at 5000 rpm for 5 minutes. The samples were analysed using HPLC method.

Results

Preparation of Flash or ODT tablets:

The taste masking of active substances is a major challenge for the successful development of ODTs. Taste masking can be achieved by many technologies through forming a thick polymer layer around the drug particle and prevent direct contact of the active substance with the taste buds. In this study, to improve the palatability of Tadalafil. Initially, tablets containing disintegrants in the same concentration were prepared. Tablets containing PVPP XL required only minimal time to become saturated during water uptake, about 30 s. A combination of microcrystalline cellulose and mannitol were used as the diluents in all formulations.

Microcrystalline cellulose can increase the porosity of tablets, thus promoting capillary action. Tablets containing 15% microcrystalline cellulose showed the shortest disintegration time. Tablets containing the higher concentrations of microcrystalline cellulose caused kind of rough surface and because the microcrystalline cellulose absorbed the saliva and did not dissolve in the oral cavity. For this reason, 15% microcrystalline cellulose was selected for the formulation of ODTs. Mannitol has good aqueous solubility, negative heats of solution, and sweet taste. These attributes decrease the sensations of roughness and bitterness, improving the perceived taste of the ODTs.

Figures below show the dissolution profiles of Tadalafil ODT versus the normal tablets of brand leader samples under different medias

a. 0.1-0.5% SLS in purified water where F2 factor is more than 90.

b. 0.1M HCL where the F2 factor is more than 58.

c. 4.5 pH buffer where the F2 is more than 94.

d. 6.8 buffer where F2 is more than 90

Analytical method Validation Studies:

Fibromyalgia and Chronic

Stability in analytical solution:

Three samples of finished product were prepared and analysed after been subjected to room temperature for 24 hours.

The data shown in the table indicates that the samples are stable in the analytical solution for 24 hours at Room temperature.

Effect of Filtration

Effect of filtration is determined by analysing the same sample by using different kind of filtration procedures as follows:

Impurities profile of Tadalafil:

Conclusion:

This study demonstrated that preparing ODT tablets and masking the taste is a real challenge for Pharmaceutical industry and end users at large.

The results demonstrated that there was no significant change in data at different analytical validation conditions. Dissolution profile results demonstrated very high similarity (F2 factor) at all recommended medias. The formulation was subjected to stability and was found stable at ICH recommended conditions.Some changes were observed in PVC/PVDC blisters of the ODTs after 10 days of exposure to 92.5% RH. These tablets thickened and increased in weight by an average of 15 mg (6.0%), and disintegration time shortened by 5 s. These results show that the ODTs absorbed moisture easily and that this reduces disintegration time. After 6 months of storage, there was no significant change in the taste, average weight, drug content, disintegration time, and or dissolution characteristics of these tablets ($P > 0.05$).

The use of Eudragit was an effective means of masking the bitter taste of the API. However, that showed a big challenge in preparing the samples for HPLC analysis as well as the HPLC column.

The experimental variables included mobile phase flow and column temperature from 25 to 40C. The standard solutions, consisting of diluent and tadalafil were injected at each condition. The optimum conditions were obtained that would yield minimum retention time and maximum resolution between the consecutive peaks and minimum relative standard deviation for six replicate injections of standard solution. The results showed that it was feasible to run the optimized HPLC method using the proposed column for tadalafil and its impurities.

Robustness parameter and acceptance criteria are shown above, was applied to method parameters. System suitability criteria were met at each of the nominal and varied conditions. All results of retention time and % differences were within the limits that set in the analytical method protocol. Since variability was low.

The understanding of the method was a major concern when developing an analytical method and even more so when dealing with impurities from complex matrices. In the presented case study a suitable approach was applied to optimize a method.

The author concluded an improved critical step taken to improve HPLC process of Chromatography by adopting a suitable sample preparation step. In addition, selection of suitable filters as well as choosing very good column to avoid such issues faced during analysis.

References

1. European Medicines Agency Science Medicines Health, Assessment report Tadalafil Generics, EMA/803097/2016, 10 November 2016.
2. Kawano Y, Ito A, Sasatsu M, Machida Y. Preparation of orally disintegrating tablets with taste-masking function: masking effect in granules prepared with correctives using the dry granulation method and evaluation of tablets prepared using the taste-masked granules. Yakugaku Zasshi. 2010;130:81–86. doi: 10.1248/yakushi.130.81.
3. Hirani JJ, Rathod DA, Vadalia KR. Orally Disintegrating Tablets. Tropical Journal of Pharmaceutical Research. April 2009; 8 (2): 161-172.
4. Anderson O, Zweidorff OK, Hjelde T. Problems when swallowing tablets. A questionnaire study from general practice. Tidsskr Nor Laegeforen. 1995;20:947–949.
5. Snyder LR, Kirkland JJ, Glajch LJ. Practical HPLC Method Development, John Wiley and Sons Inc., New York, 1988; 3, 2-21.
6. The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, Quality Guideline Q2(R1) Validation of Analytical procedures: Text and Methodology, 2005.
7. Douroumis D. Orally disintegrating dosage forms and taste-masking technologies; 2010. Expert Opin Drug Deliv. 2011; 8:665–675. doi: 10.1517/17425247.2011.566553.
8. Kawano Y, Ito A, Sasatsu M, Machida Y, Onishi H. Preparation and evaluation of taste masked orally disintegrating tablets with granules made by the wet granulation method. Yakugaku Zasshi. 2010; 130:1737–1742. doi: 10.1248/yakushi.130.1737.
9. Snyder LR, Kirkland JJ, Glajch LJ. Practical HPLC Method Development; 2nd Edn; John Wiley & Sons Inc., New York, 1997.
10. Sheshala R, Khan N, Darwis Y. Formulation and optimization of orally disintegrating tablets of sumatriptan succinate. Chem Pharm Bull. 2011;59:920–928. doi: 10.1248/cpb.59.920.
11. Bhise K, Shaikh S, Bora D. Taste mask, design and evaluation of an oral formulation using ion exchange resin as drug carrier. AAPS PharmSciTech. 2008;9:557–562. doi: 10.1208/s12249-008-9056-6

12. Szejtli J, Szente L. Elimination of bitter, disgusting tastes of drugs and foods by cyclodextrins. Eur J Pharm Biopharm. 2005;61:115–125. doi: 10.1016/j.ejpb.2005.05.006.

13. Ishikawa T, Watanabe 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;47:1451–1454. doi: 10.1248/cpb.47.1451.

14. Yan YD, Woo JS, Kang JH, Yong CS, Choi HG. Preparation and evaluation of taste-masked donepezil hydrochloride orally disintegrating tablets. Biol Pharm Bull. 2010;33:1364–1370. doi: 10.1248/bpb.33.1364.

15. Löbenberg R, Krämer J, Shah VP, Amidon GL, Dressman JB. Dissolution testing as a prognostic tool for oral drug absorption: dissolution behavior of glibenclamide. Pharm Res. 2000;17:439–444. doi: 10.1023/A:1007529020774.

16. Ishikawa T, Mukai B, Shiraishi S, Utoguchi N, Fujii M, Matsumoto M, et al. Preparation of rapidly disintegrating tablet using new types of microcrystalline cellulose (PH-M series) and low substituted-hydroxypropylcellulose or spherical sugar granules by direct compression method. Chem Pharm Bull. 2001;49:134–139. doi: 10.1248/cpb.49.134.

17. Battu SK, Repka MA, Majumdar S, Madhusudan RY. Formulation and evaluation of rapidly disintegrating fenoverine tablets: effect of superdisintegrants. Drug Dev Ind Pharm. 2007;33:1225–1232. doi: 10.1080/03639040701377888.

18. Morita Y, Tsushima Y, Termoz R, Ajioka J, Takayama K. Evaluation of disintegration time of rapidly disintegrating tablets via a novel method utilizing a CCD camera. Chem Pharm Bull. 2002;50:1181–1186. doi: 10.1248/cpb.50.1181

19. Rawas-Qalaji MM, Simons FE, Simons KJ. Fast-disintegrating sublingual tablets: effect of epinephrine load on tablet characteristics. AAPS PharmSciTech. 2006;7:E41. doi: 10.1208/pt070241.

20. Shibata Y, Yamamoto Y, Fujii M, Kondoh M, Watanabe Y. A novel method for predicting disintegration time in the mouth of rapidly disintegrating tablet by compaction analysis using TabAll. Chem Pharm Bull. 2004;52:1394–1395. doi: 10.1248/cpb.52.1394.

21. Narazaki R, Harada T, Takami N, Kato Y, Ohwaki T. A new method for disintegration studies of rapid disintegrating tablets. Chem Pharm Bull. 2004;52:704–707. doi: 10.1248/cpb.52.704.

22. Azzam R Ali (Hussein) , Ibrahim I Duraidi, Munib M Saket. Column High-Performance Liquid Chromatographic Method for the Simultaneous Determination of

23. Rosiglitazone and Metformin in a Pharmaceutical Preparation. Journal of AOAC INTERNATIONAL, Volume 92, Issue 1, 1 January 2009, Pages 119–124.

24. Paz O, Saha, Azzam Hussein, John B. Simultaneous Determination of 23 Azo Dyes in Paprika by Gas Chromatography-Mass Spectrometry September 2016Food Analytical Methods 10(4).

25. Eyad, Reyad, Azzam Ali(Hussein). High-performance liquid chromatographic determination of simvastatin in medical drugs, January 2006Journal of Analytical Chemistry 61(1)