High Throughput Analysis of Orlistat® Drug Standard and Corresponding Non-Prescription Over-The-Counter Drug alli® using TSK-GEL® ODS-140HTP, 2.3µm Columns

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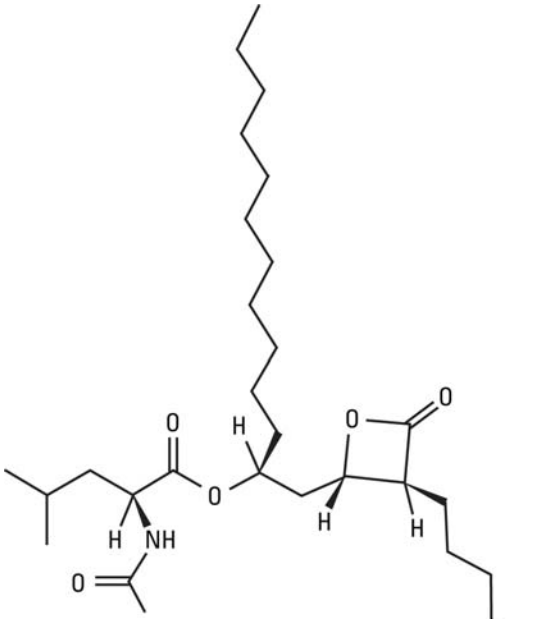
Introduction

Orlistat is marketed by Roche as a prescription drug under the trade name Xenical® and as an over-the-counter drug under the trade name alli by GlaxoSmithKline. Orlistat is a lipstatin drug used to treat obesity by preventing the adsorption of dietary fats[1].



Orlistat

[1]Bodkin J, Humphries E, McLeod M (2003). "The total synthesis of (−)-tetrahydrolipstatin". *Australian Journal of Chemistry* 56 (8): 795–803. doi:10.1071/CH03121

Scope of generic drugs

- Pharmaceuticals are among the most highly regulated products in the United States.
- Newly developed brand drugs have patent protection until the expiration date.
- After a patent expires many generic manufacturers may produce it as a less expensive product.
- An estimated $64 billion of pharmaceutical products are coming off-patent in the near future[2].
- The retail market for generic pharmaceuticals is also expected to increase, particularly from the competitive pressure of producing quality products at lower cost.

[2]http://www.fda.gov/NewsEvents/ Speeches/ucm051966.htm

Challenge to generic manufacturers

- Orlistat has recently come off of patent protection[3].
- alli is available in the market as the FDA approved non-prescription weight loss aid[4,5].
- The drug is used for prevention of lipid absorption by inhibition of pancreatic lipase[6].
- The challenge for generic makers is to develop validated chromatographic methods for a number of similar drugs coming off patent protection in the near future.

[3]http://drugtopics.modernmedicine.com/drugtopics/Supplements/Drug-patent-expirations-2007 2009/ArticleStandard /Article /detail/414709

[4]Pommier A, Pons M, Kocienski P (1995). "The first total synthesis of (-)-lipstatin". Journal of Organic Chemistry 60 (22): 7334–7339. doi:10.1021/jo00127a045.

[5]Padwal R, Li SK, Lau DC (2004). "Long-term pharmacotherapy for obesity and overweight". Cochrane Database Syst Rev (3): CD004094. doi:10.1002/14651858.CD004094.pub2. PMID 15266516.

[6]Barbier P, Schneider F (1987). "Syntheses of tetrahydrolipstatin and absolute configuration of tetrahydrolipstatin and lipstatin". Helvetica Chimica Acta 70 (1): 196–202. doi:10.1002/hlca.19870700124.

Challenge to generic manufacturers

- Reversed phase liquid chromatography (RPC) is an analytical technique widely used in the R&D and QC departments of drug manufacturers.
- In this era of high throughput analysis, the need to obtain lower retention times while maintaining or improving resolution from closely eluting impurities is very important for quality control analysis.
- Here we report the separation of Orlistat and the corresponding OTC drug alli using a TSKgel® ODS-140HTP, 2.3µm, 2.1mm ID x 5cm column.

Objective

To show the usefulness of the silica based TSKgel ODS-140HTP, 2.3µm, 2.1mm ID x 5cm reversed phase column for high throughput analysis of Orlistat from a FDA approved over the counter drug alli drug standard using a conventional HPLC system.

Table 1: Properties of TSK-GEL ODS-140HTP columns

TSK-GEL ODS-140HTP	
Pore size (silica):	140Å
Endcapped:	yes
Particle size:	2.3µm
pH stability:	2.0 - 7.5
Functional group:	C18 (polymeric bonding chemistry)
% carbon:	8%

Material and methods

All analyses were carried out using an Agilent 1100 HPLC system run by Chemstation (ver B.03.01).

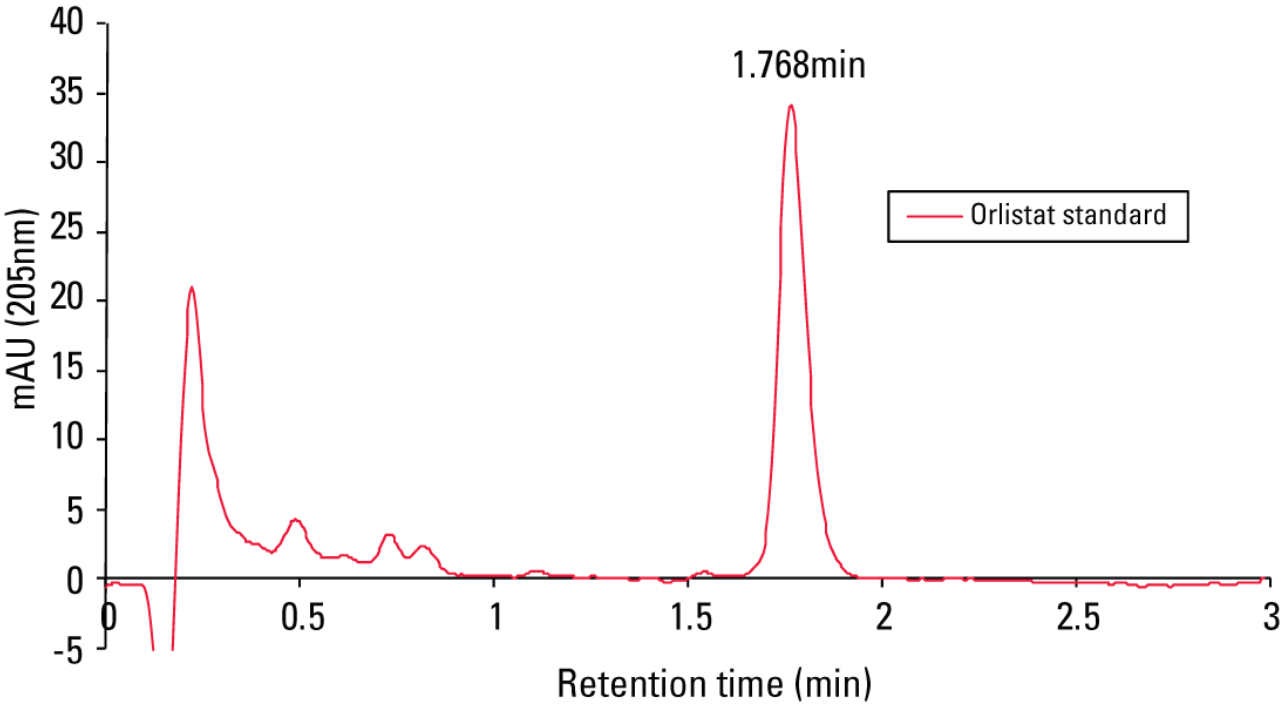
Optimal chromatographic conditions:

- Columns:
  - TSKgel ODS-140HTP, 2.3µm, 2.1mm ID x 5cm
  - Hypersil GOLD® C18, 1.9µm, 2.1mm ID x 5cm
  - Luna® C18(2)-HST, 2.5µm, 2.0mm ID x 5cm
- Detection: 205nm
- Column temp: 40˚C
- Flow rate: 1.5mL/min unless mentioned otherwise
- Injection volume: 10µL
- Mobile phase (Isocratic): 70% ACN in H_20 with 0.15% TFA

Material and methods

- High purity Sigma-Aldrich brand Orlistat was used for the preparation of stock standards.
- The standards were filtered through a 0.45µm membrane before injecting into the column.
- Working standards were prepared by dilution of the stock standard in H_2O or 50% MeOH as necessary.
- The over-the counter drug alli was purchased from a local pharmacy.
- A total of 0.1145gm of the white, cube shaped drug material was weighed out of a single 60mg capsule, dissolved in 50% MeOH in H_2O, filtered through a 0.45µm membrane and stored at -20°C.
- The working standards were prepared by 1:10 dilution in 50% MeOH and directly used for the chromatographic analysis.

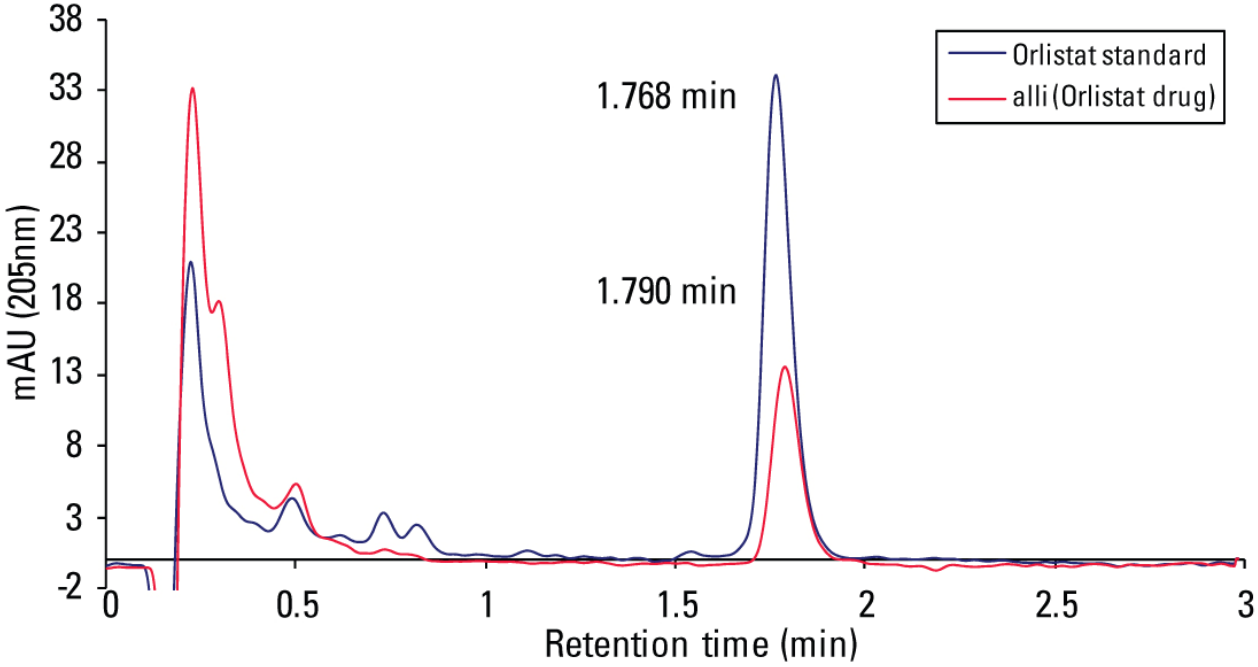
Figure 1: Isocratic elution of an Orlistat standard using a TSKgel ODS-140HTP column



Column:	TSKgel ODS-140HTP, 2.1mm ID x 5cm
Mobile phase:	70% ACN with 0.15% TFA
Flow rate:	1.5mL/min
Detection:	UV@205nm
Temperature:	40°C
Injection vol.:	10µL
Sample:	orlistat, 100µg/mL

Orlistat eluted with low retention time (< 2 minutes).

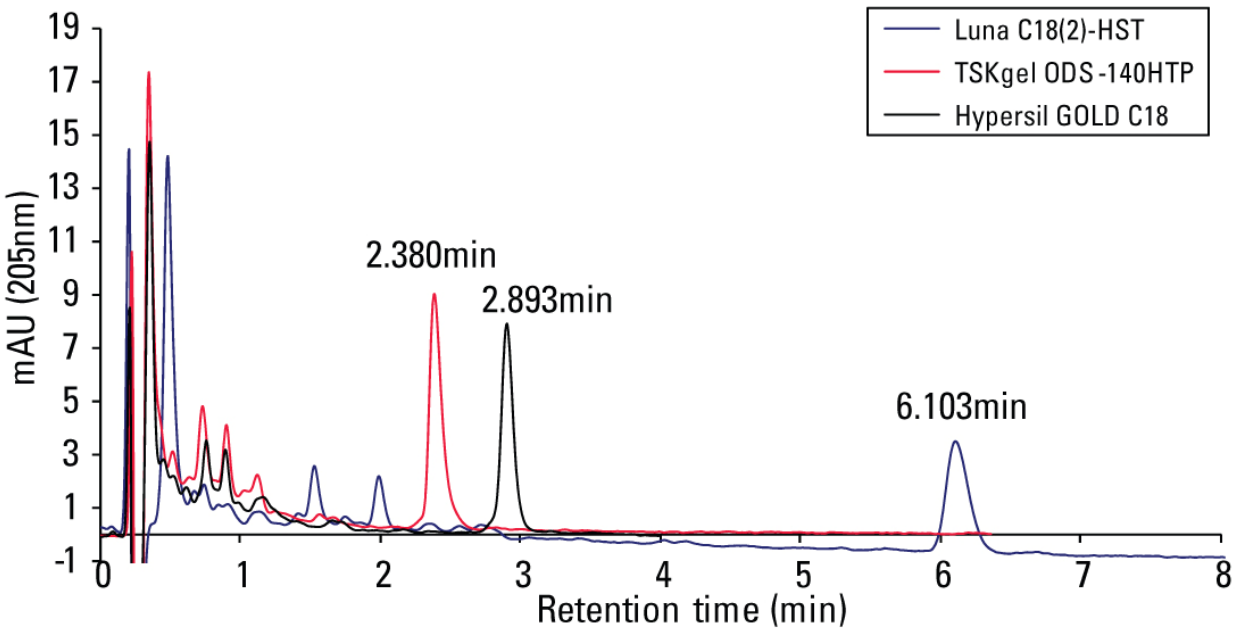
Figure 2: Separation of Orlistat from alli using a TSKgel ODS-140HTP column



Column:	TSKgel ODS-140HTP, 2.1mm ID x 5cm
Mobile phase:	70% ACN with 0.15% TFA
Flow rate:	1.5mL/min
Detection:	UV@205nm
Temperature:	40°C
Injection vol.:	10µL
Samples:	orlistat standard and alli

- **The Orlistat standard peak eluted at 1.768 minute, while the Orlistat sample from alli eluted at 1.790 minute.**
- **This study shows that the column can be used for the method development of these generic drugs.**

Figure 3: Comparative study of the elution profile of the off-patent drug Orlistat



Columns:	TSKgel ODS-140HTP, 2.1mm ID x 5cm Luna C18(2)-HST, 2.0mm ID x 5cm Hypersil GOLD C18, 2.1mm ID x 5cm
Mobile phase:	70% ACN with 0.15% TFA
Flow rate:	1.2mL/min
Detection:	UV@205nm
Temperature:	40°C
Injection vol.:	10µL
Sample:	orlistat, 100µg/mL

The TSKgel ODS-140HTP column yielded the shortest retention times in comparison to the other two competitive columns tested under identical chromatographic conditions.

Conclusions

- The TSKgel ODS-140HTP, 2.3µm, 2.1mm ID x 5cm reversed phase column was used for the analysis of an Orlistat drug standard.
- Orlistat eluted with a short retention time (<2 minutes).
- The TSKgel ODS-140HTP reversed phase column was used for the separation of Orlistat, the active pharmaceutical ingredient (API) from the OTC drug formulation alli, without any interference from other ingredients present in the formulation.
- This study shows that a TSKgel ODS-140HTP column can be used by generic manufacturers for the separation of similar drugs coming off patent in the future.