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Quantitative Determination of Drugs in Dosage Forms as a Tool of Quality Control Studies

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1. Introduction

Pharmaceutical stability may be defined as the capability of a particular formulation, in a specific container/closure system, to remain within its physical, chemical, microbiological, therapeutic, and toxicological specifications, during transport, storage and use. Chemical degradation may result in a loss of potency or an increase in drug toxicity, so that clinical use of a medicine must be unacceptable if the degradation is relatively great. When a drug dosage form is altered (by dissolution, pulverization, or addition to other materials) or the environment of the drug is modified by changes in storage conditions, the stability of a drug may be affected [1-5]. Although there are exceptions, 90% of labeled potency generally is recognized as the minimum acceptable potency level (Gennaro, 2000).

Stability testing forms an important part of the process of drug development; it provides evidence on how the quality of drug substance or drug product varies with time under the influence of a variety of environmental factors, such as humidity, temperature, and light. The stability studies of drugs can be performed at the original product ("real-time" tests or long-term tests at specific temperatures and relative humidity representing storage conditions experienced in the distribution chain of the climatic zone(s) of the country or region of the world concerned; accelerated stability tests; pharmacies storage tests) or at remainder doses of these products. The chemical stability is evaluated by testing quantity of drug at different time during the storage (Lund, 1994; USP, 2007).

The aim of the stability studies is to determine the shelf life of the product and its optimum storage conditions (Connors et al., 1986; Lund, 1994; The Sixth ICH International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use [ICH], 2003; The United States Pharmacopeia [USP], 2007; Watson, 2005; Yoshioka, 2000).

Therefore, the authors have been developing and validating HPTLC methods with the aim of quantification of drugs in dosage forms, suitable for stability and quality control studies, as at original products as at its remainder doses.

2. Drugs

Some drugs analyzed by HPTLC developed methods had been Fluphenazine, Haloperidol and L-DOPA.

2.1 Fluphenazine

Fluphenazine is a phenothiazine antipsychotic agent. The drug is a propylpiperazine derivative of phenothiazine (Delgado et al., 1998; Hardman & Limbird, 2006; Mc Evoy, 2006; Sweetman, 2003).

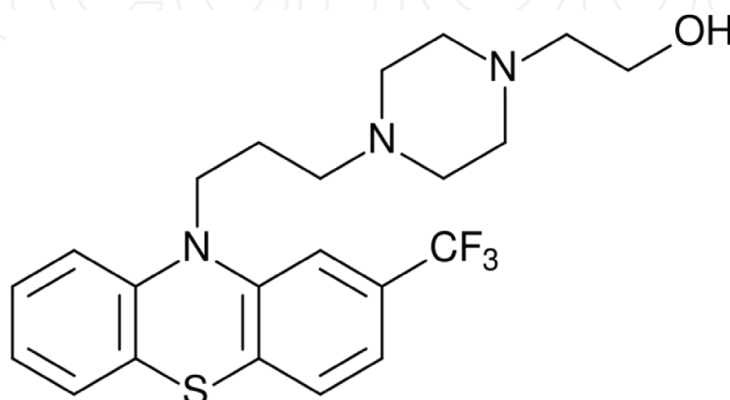


Fig. 1. Chemical structure of Fluphenazine

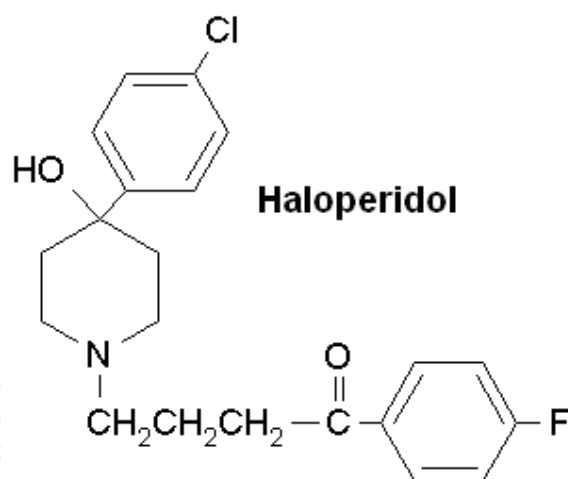


Fig. 2. Chemical structure of Haloperidol

Drug therapy with fluphenazine is integral for the management of acute psychotic episodes with violent behavior in patients with schizophrenia and generally is required for long-term stabilization to improve symptoms between episodes and to minimize the risk of recurrent acute episodes (Hardman & Limbird, 2006; Mc Evoy, 2006; Sweetman, 2003).

Fluphenazine hydrochloride, decanoate, and enantate are all sensitive to light. Therefore, it is very important to determine the quantity of fluphenazine in its dosage forms because in the presence of light, photolysis occur rapidly, resulting in drug loss and potency reduction (Delgado et al., 1998; Hardman & Limbird, 2006; Mc Evoy, 2006; Moffat et al., 2004; Sweetman, 2003).

2.2 Haloperidol

Haloperidol, a butyrophenone derivative, is used for the symptomatic management of psychotic disorders, in the same way that fluphenazine (Delgado et al., 1998; Hardman & Limbird, 2006; Mc Evoy, 2006; Sweetman, 2003).

When haloperidol injection is used, dose is depending on the severity of the illness, the age of the patient and on their response to the pharmacotherapy. Therefore, sometimes the dose corresponded only to a portion of the injection. The portion which is not used is stored for the next administration or is discarded (Delgado et al., 1998; Hardman & Limbird, 2006; Mc Evoy, 2006). The stability of this portion is unknown.

2.3 L-DOPA

L-DOPA, the levorotatory isomer of dihydroxyphenylalanine, a natural amino acid, is the precursor of the neurotransmitter dopamine.

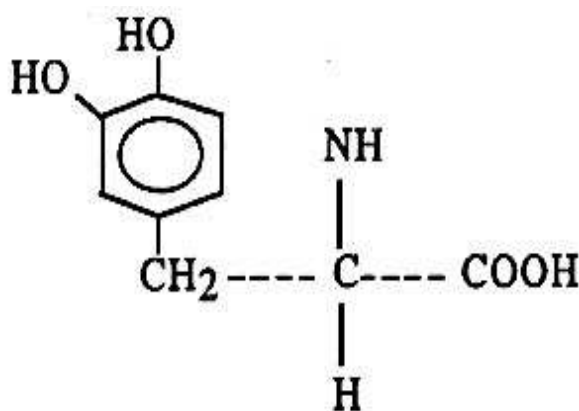


Fig. 3. Chemical structure of L-DOPA

The actions of L-DOPA are mainly those of dopamine. Unlike dopamine, L-DOPA can readily enter the Central Nervous System and is used in the treatment of conditions, such as Parkinson's disease, which are associated with depletion of dopamine in the brain (Delgado et al., 1998; Hardman & Limbird, 2006; Mc Evoy, 2006, Sweetman, 2003). L-DOPA is considered by many clinicians the drug of choice in the management of idiopathic parkinsonian syndrome (Mc Evoy, 2006).

It is very important to determine the quantity of L-DOPA in its dosage forms, because, in the presence of moisture or atmospheric oxygen, it is rapidly oxidized resulting in drug loss and potency reduction (Carstensen, 1990; Mc Evoy, 2006; USP, 2007; Sweetman, 2003).

3. Methods

Some methods have been reported for the analysis of fluphenazine, haloperidol and L-DOPA in pharmaceutical preparations or in biological fluids. These methods include: spectrophotometry (Blanco et al., 2000; Damiani et al., 2005; Karpinska et al., 2005; Madrakian et al., 2004; Madrakian et al., 2006; Marcolino-Junior et al., 2001; Nagaraja et al., 2001; Nagaralli et al., 2002; Nour El-Dien et al., 2005; Pistonesi et al., 2004; Talebpour et al., 2005), gas chromatography (Jemal et al., 2005), liquid chromatography (Ali & Aboul-Enein, 2005; Chaná et al., 2004; Crevoisier et al., 2003; Fernández et al., 2001; Karimi et al., 2006; Kircherr & Kühn-Velten, 2006; Lea et al., 1982; Nyholm et al., 2002; Sagar & Smyth, 2000;

Saxer et al., 2004; Trabelsi et al., 2002; Wang & Fang, 2006), electrophoresis (Zhang et al., 2001) and voltammetry (Maia et al., 2005). Nevertheless, these methods have often suffered from diverse disadvantages with regard to cost or selectivity, with complex sample preparation procedures, and long analysis time.

Also, one method by TLC was found for determination of fluphenazine hydrochloride in coated tablets, but not in ampoules (Maslanka & Krzek, 2005). Only one paper of stability of haloperidol in injections is discussed in literature, but this paper deals with the stability of haloperidol in 5% dextrose injection (Das Gupta & Stewart, 1982).

3.1 High performance thin layer chromatography (HPTLC)

High performance of HPTLC is due to its fastness, solvent economy and high throughput of samples. Chromatography of samples simultaneously with standards is another advantage, allowing to run up to 60 spots simultaneously (27 samples plus standards by each side of the plate). Sensitivity of HPTLC is normally in the range of nanograms in absorbance and picograms in fluorescence mode.

The authors have performed some works using HPTLC for quantitative determination of drugs in biological fluids (Mennickent et al., 2003, 2007a, 2007b, 2009, 2010a, 2010b) and in dosage forms (de Diego et al., 2007a, 2007b, 2010a, 2010b; Mennickent et al., 2007a, 2007b, 2007c, 2010), with exact and reliable results.

The HPTLC methods developed are simple, rapid, with low LOD and LOQ values, with very good accuracy and precision, with robustness, and economical.

3.1.1 Method for fluphenazine injections

For the quantification of fluphenazine in injections, the method was linear in the range of 100 ng/band to 500 ng/band ($r=0.998$). The limit of detection (LOD) and limit of quantification (LOQ) were 1.45 ng/band and 4.40 ng/band, respectively. The intra-assay and inter-assay precision, expressed as the relative standard deviation (RSD), were in the range of 0.73%-1.77% ($n=3$) and 1.18%-1.86% ($n=9$), respectively. The recovery of fluphenazine hydrochloride was in the range 98.29% and 101.53%, with a RSD not higher than 1.87%. The method was selective for fluphenazine hydrochloride from the preservatives of the injections (R_f for fluphenazine hydrochloride was 0.33, whereas parabens run to the solvent front) (Fig. 4 and Fig. 5).

Stability-indicating capability of the HPTLC assay was studied by forced decomposition of 5 mL of a solution of fluphenazine 1 mg/mL, with 10 mL of 0.1 N hydrochloric acid, 10 mL of 0.1 N sodium hydroxide and 10 mL of 3% H_2O_2 . The mixtures with NaOH and with HCl were heated on hot plates at 60°C for 60 minutes. The mixture with H_2O_2 was stored at room temperature (25°C) for 60 minutes. Then, each mixture was diluted to 100 ng/ μ L with ethanol and analyzed.

Also, stability-indicating capability of the assay was proved by conducting forced degradation conditions of UV and VIS radiation on fluphenazine standard, as a solution of 100 ng/ μ L.

One degradation product was found after treatment of fluphenazine with HCl, and two degradation products were found after treatment with NaOH. R_f for fluphenazine was 0.30, whereas R_f for degradation product with HCl was 0.01, and R_f for degradation products with NaOH were 0.03 and 0.23 respectively. No degradation product was found with H_2O_2 (Fig. 6).

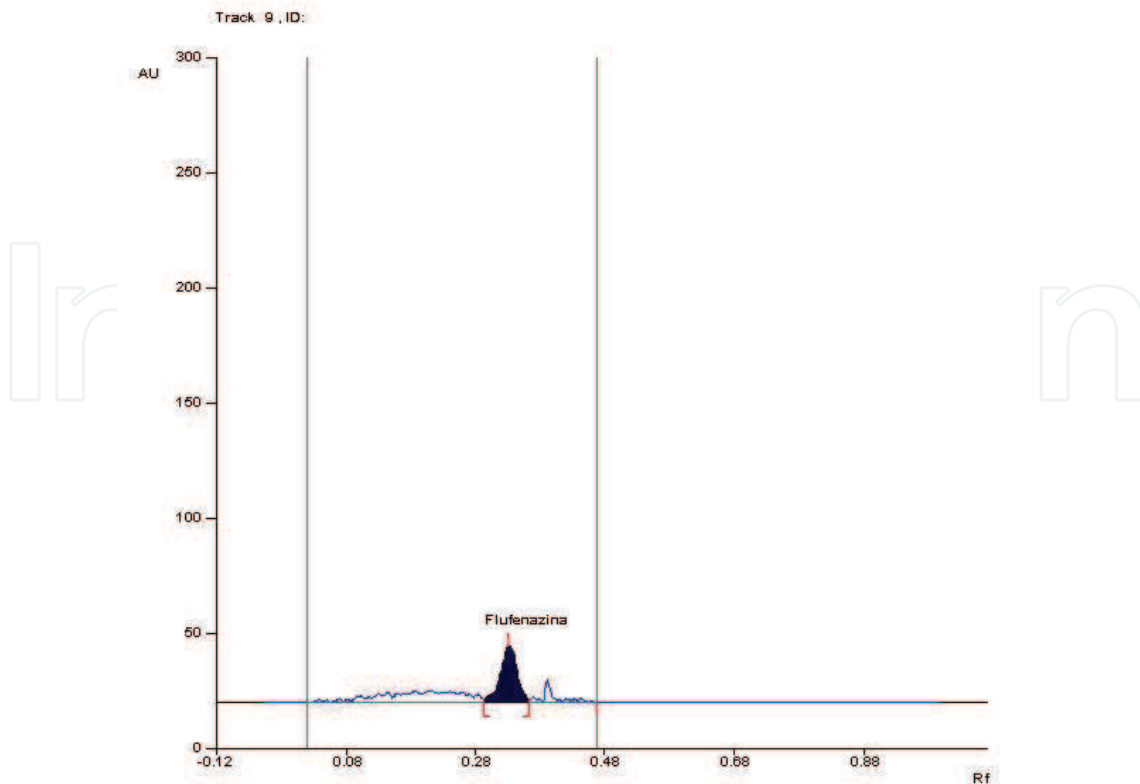


Fig. 4. Selectivity of the method. Study with parabens. Peak observed: fluphenazine. Rf: retarding factor. AU: absorbance unit

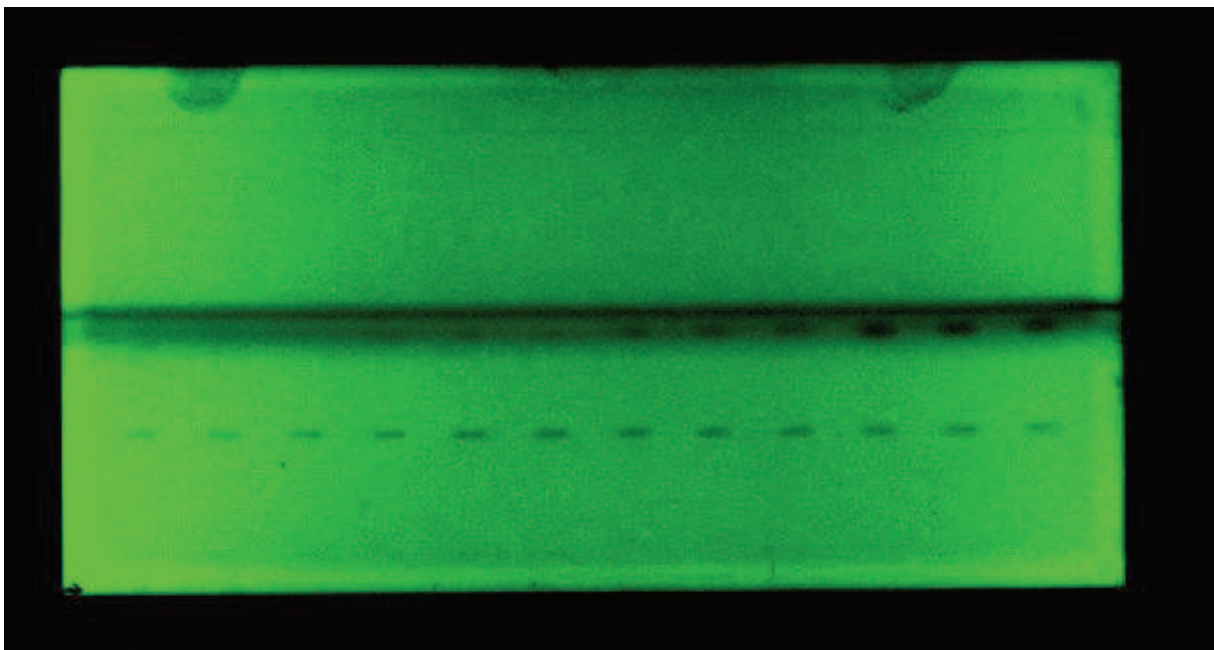


Fig. 5. Picture (video store, CAMAG) of plate at selectivity with parabens. Tracks 1-3 (from left to right of the plate) : fluphenazine hydrochloride; tracks 4-6: fluphenazine hydrochloride + methylparaben; tracks 7-9: fluphenazine hydrochloride + propylparaben; tracks 10-12: fluphenazine hydrochloride + methylparaben + propylparaben. Bands of parabens can be observed at the solvent front

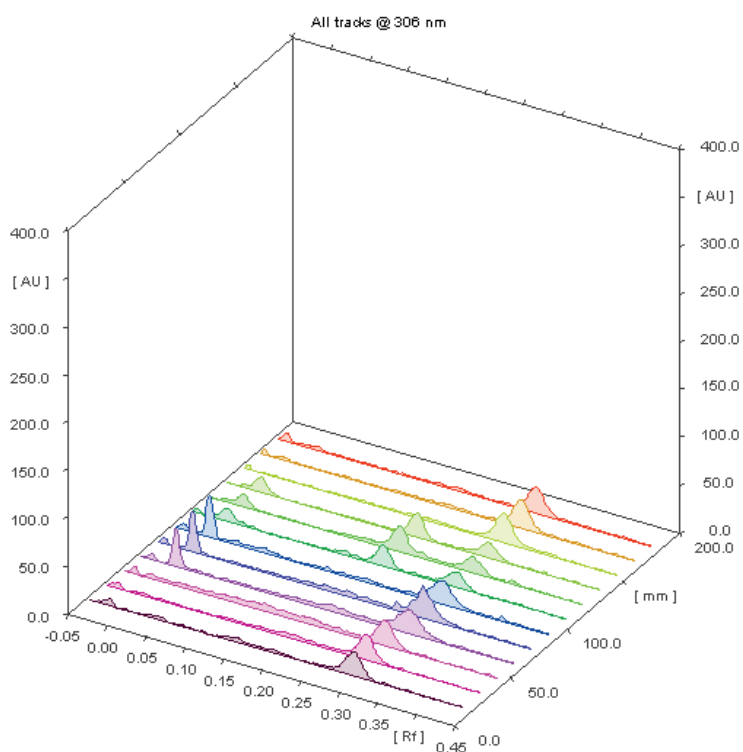


Fig. 6. Degradation study of fluphenazine with HCl, with NaOH and with H₂O₂. Tracks 1-3 (from bottom side to the upper side): fluphenazine; tracks 4-6: fluphenazine + HCl; tracks 7-9: fluphenazine + NaOH; track 10-12: fluphenazine + H₂O₂. Rf peak fluphenazine = 0.30. Other peaks at tracks 4-9: degradation products. Rf: retarding factor. AU: absorbance unit

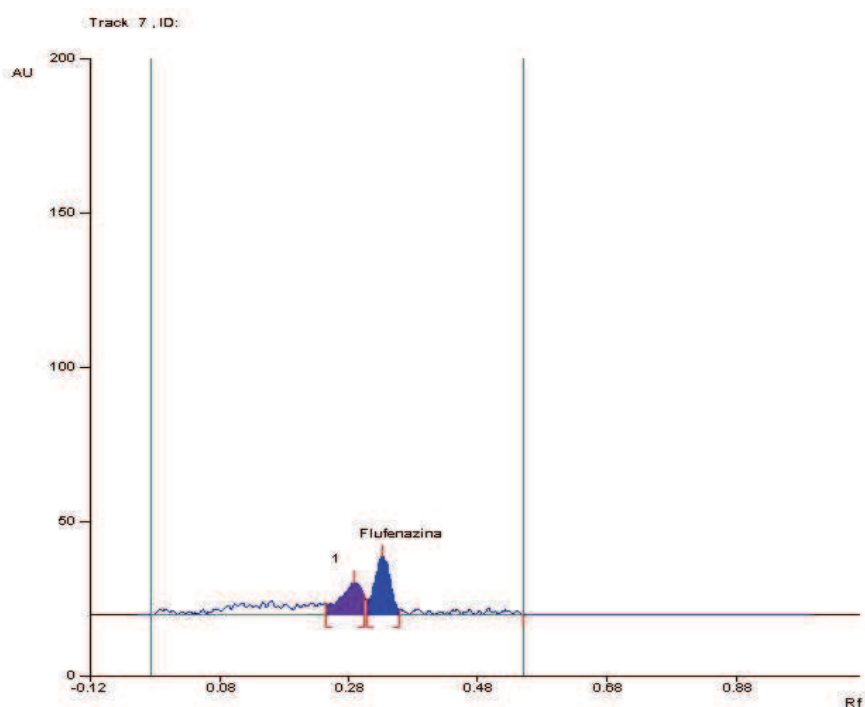


Fig. 7. Degradation study of fluphenazine with VIS radiation. Peak 1 (from left to right): fluphenazine; peak 2: degradation product. Rf: retarding factor: AU: absorbance unit

When the drug was exposed to forced degradation with VIS radiation, another peak different to the peak of fluphenazine was found, therefore it could be a degradation product. R_f for fluphenazine = 0.30 and R_f for degradation product = 0.56 (Fig. 7). One of the products of photolysis mentioned in literature is a sulphoxide (Lund, 1994).

Values for precision study of the method can be observed at the Table 1.

Concentration (ng/uL)	Relative standard deviation (RSD), %	
	Intraassay precision ^a	Intermediate precision ^b
100	1.77	1.86
300	1.64	1.47
500	0.73	1.18

^a n= 3; analyzed on the same day (for each concentration)

^b n= 9; analyzed on three different days (for each concentration)

Table 1. Precision of the HPTLC method for fluphenazine injections

Values founded for the accuracy of the method are presented at the Table 2.

Added concentration (ng/uL)	Found concentration (ng/uL) ^a	Accuracy, % ^b	RSD, % ^c
Intraassay (n=9)			
80	79.90 ± 1.31	99.87	1.64
100	100.45 ± 1.10	100.45	1.10
120	121.84 ± 2.28	101.53	1.87
Interassay (n=27)			
80	78.63 ± 1.34	98.29	1.71
100	99.74 ± 1.65	99.74	1.65
120	120.90 ± 1.83	100.75	1.52

^a Each value is the mean ± standard deviation.

^b (Founded concentration/ added concentration) × 100.

^c Relative standard deviation (coefficient of variation).

Table 2. Method accuracy

3.1.2 Method for haloperidol injections

For the quantification of haloperidol in injections, the method was linear between 10ng/band to 100 ng/band ($r = 0.999$), the method was selective between haloperidol and the parabens, the preservatives in haloperidol lactate injection (R_f for haloperidol was 0.70, whereas parabens run to the solvent front) (Fig. 8-10). RSD for precision was ≤ 1.92%, and accuracy was from 98.59% to 101.90% of recovery. LOD was 0.89 ng/band and LOQ was 2.71 ng/band.

Stability-indicating capability of the HPTLC assay was established by forced decomposition of 5 mL of a solution of haloperidol lactate 1 mg/mL, with 10 mL of 0.1 N hydrochloric acid and 10 mL of 0.1 N sodium hydroxide. The mixture was heated on a hot plate at 60°C for 60 minutes, cooled to room temperature, diluted to 100 ng/uL with methanol and analyzed.

Also, stability-indicating capability of the assay was proved by conducting forced degradation conditions of VIS radiation on haloperidol standard.

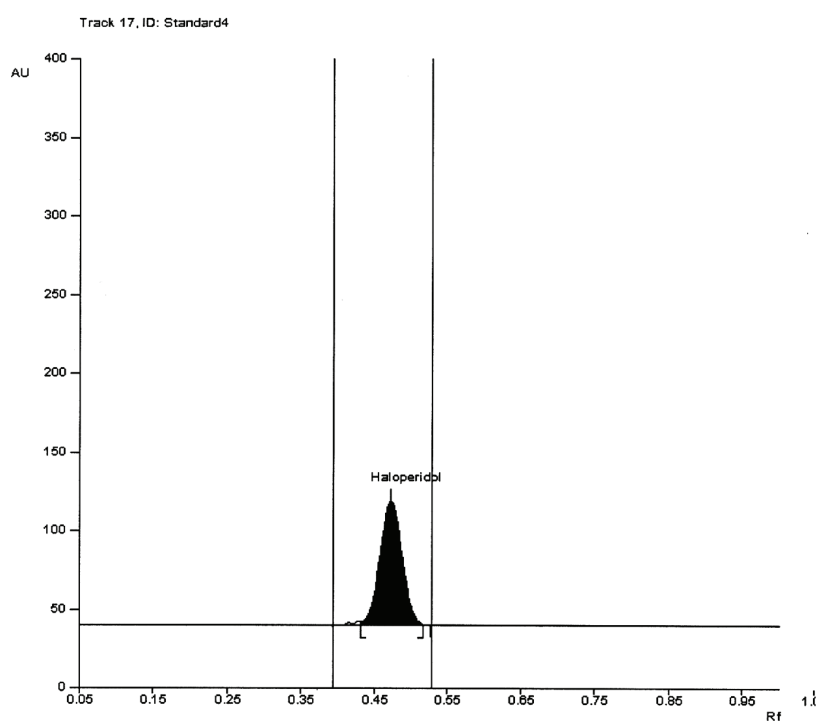


Fig. 8. Peak of haloperidol. Rf: retarding factor: AU: absorbance unit. Solution concentration: 80 ng/uL

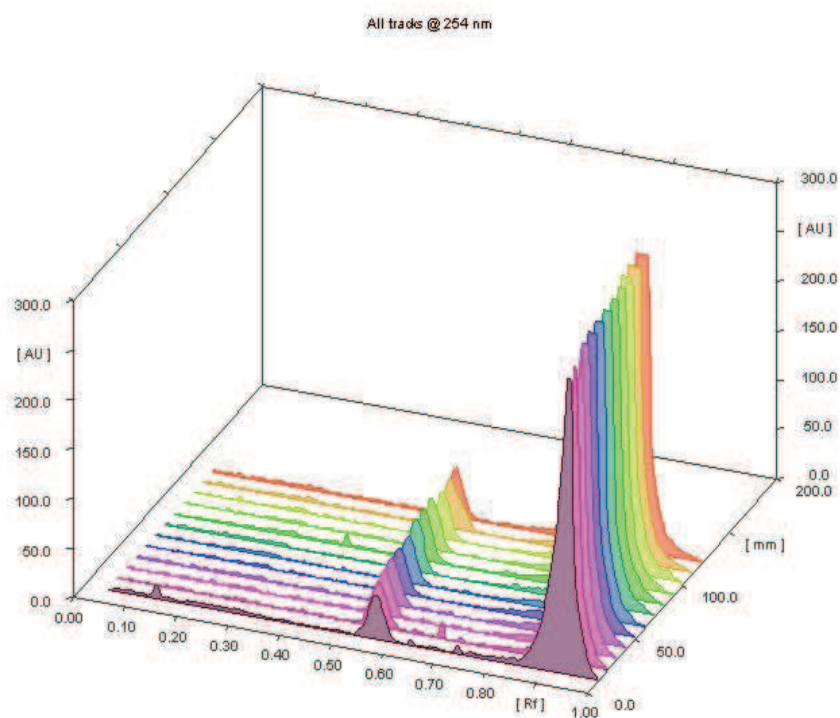


Fig. 9. Selectivity of the method. Study with parabens. Tracks 1-3 (from the bottom side to the upper side): haloperidol; tracks 4-6: haloperidol + methylparaben; tracks 7-9: haloperidol + propylparaben; tracks 10-12: haloperidol + methylparaben + propylparaben. Peak 1 (from left to right): haloperidol; peak 2: solvent front. Rf: retarding factor. AU: absorbance unit

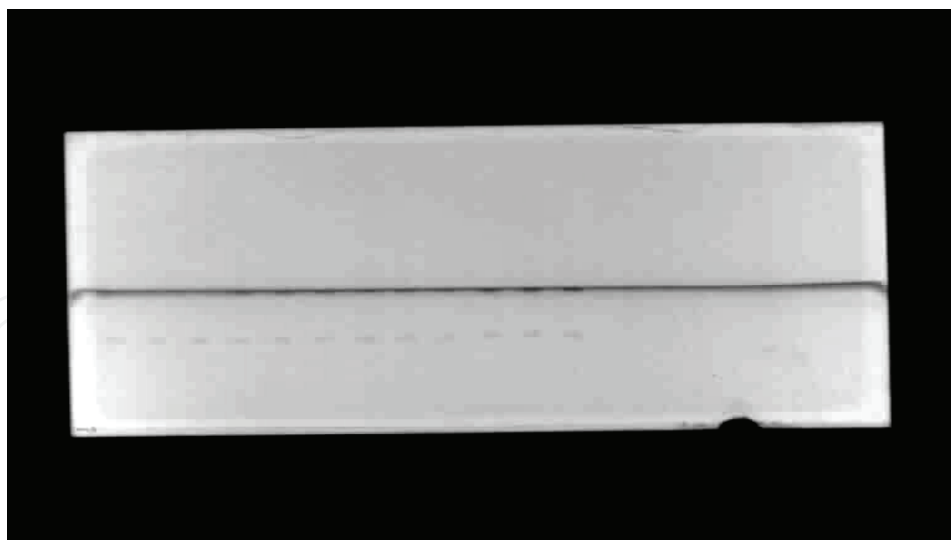


Fig. 10. Picture (video store, CAMAG) of plate at selectivity between haloperidol and parabens. Tracks 1-3: haloperidol; tracks 4-6: haloperidol + methylparaben; tracks 7-9: haloperidol + propylparaben; tracks 10-12: haloperidol + methylparaben + propylparaben. Bands of parabens can be observed at the solvent front

After treatment of haloperidol lactate with acid none degradation product was found. However, after treatment with basic, one minor peak was found, which probably correspond to a degradation product, with a resolution of 2.4 between haloperidol and another peak (Fig. 11)

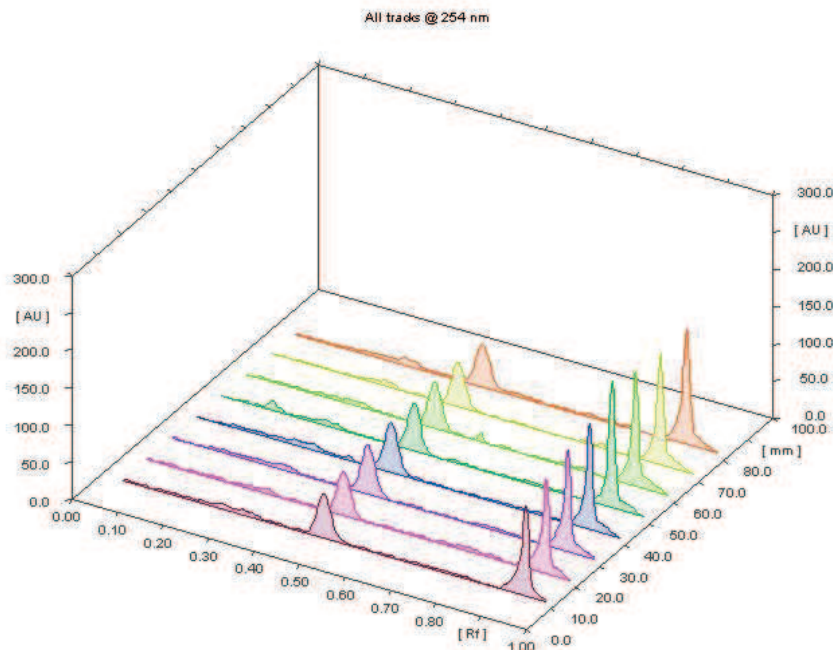


Fig. 11. Selectivity of the method. Study at forced degradation of haloperidol with 0.1 N HCl and 0.1 N NaOH. Tracks 1,2,7,8 (from the bottom side to the upper side): haloperidol; tracks: 3-4: haloperidol + HCl; tracks 5-6: haloperidol + NaOH. Peak 1 (from left to right): haloperidol; peak 2: solvent front. Minor peak at tracks 5-6: degradation products. Rf: retarding factor; AU: absorbance unit

When the drug was exposed to forced degradation with VIS radiation, no degradation product was found.

The degradation products for haloperidol mentioned in literature are acrolein, chlorobenzene, p-fluorobenzaldehyde, p-fluoroacetophenone, p-fluorophenyl propenyl ketone, when haloperidol was irradiated with a sterilising dose of gamma radiation (Lund et al., 1994). Another studies found 4-(4-chlorophenyl)-4-hydroxypiperidine and 4-fluorobenzoic acid, presumed to be hydrolytic products of haloperidol (Jemal et al., 2005; Karipnska et al., 2005) and 4-[4-(4-chlorophenyl)-4-hydroxy-1-piperidinyl]-1-(4-fluorophenyl)-1-butanone N-oxide; and 4-[4-(4-chlorophenyl)-4-hydroxy-1-piperidinyl]-1-(4-hydroxyphenyl)-1-butanone; 4-[4-(4-chlorophenyl)-3,6-dihydro-1(2H)-piperidinyl]-1-(4-fluorophenyl)-1-butanone (Lund et al., 1994).

Values for the precision study are shown at the Table 3.

Concentration (ng/uL)	Relative standard deviation (RSD), %		
	Instrumental precision ^a	Intraassay precision ^b	Intermediate precision ^c
10	0.81	1.31	1.92
50	0.37	1.74	1.53
100	0.51	0.38	1.11

^a n= 10; analyzed on the same day

^b n= 5; analyzed on the same day (for each concentration)

^c n= 9; analyzed on three different days (for each concentration)

Table 3. Precision of the method

Values for the accuracy of the method can be observed at the Table 4.

Added concentration (ng/uL)	Found concentration (ng/uL) ^a	Accuracy, % ^b	
Intraassay (n=9)			
80	78.87 ± 2.98	98.59	3.78
100	101.21 ± 3.78	101.21	3.74
120	119.05 ± 1.75	99.21	1.47
Interassay (n=27)			
80	81.52 ± 3.59	101.90	4.40
100	99.74 ± 4.41	99.74	4.42
120	119.35 ± 5.37	99.46	4.50

^a Each value is the mean ± standard deviation.;

^b (Founded concentration/ added concentration) x 100;

^c Relative standard deviation (coefficient of variation).

Table 4. Method accuracy

Stability study of haloperidol lactate injection 5mg /mL was realized at the following conditions: 25 ± 2 °C, because it is the more common temperature founded at hospitals in Chile and is the temperature mentioned by ICH guidelines for stability studies at dosage forms; and refrigeration temperature (8 ± 1 °C) in its original glass ampoules after it was opened, removed a portion of drug, and sealed with Teflon. The samples at room temperature were stored under light exposure and light protection. The study was performed over 15 days.

Samples were taken at appropriate time intervals (0, 3, 5, 7, 10 and 15 days), and analyzed in duplicate by HPTLC to determine haloperidol concentration. For stability study, 100 μ L of the haloperidol lactate injection 5 mg/mL was transferred to a 10 mL volumetric flask and diluted with methanol to volume (final concentration of 50 ng/ μ L).

The percentage of haloperidol remaining after each interval was determined by comparing the concentration at that time with the initial haloperidol concentration, measured before storage ($t = 0$) at the different conditions. Haloperidol lactate injections, when stored at 25 ± 2 °C under light exposure and light protection, and when stored at refrigeration temperature (8 ± 1 °C) in original glass ampoules opened and after closed with Teflon retained at least 90% of the initial concentration over 15 days (Table 5).

Storage time (days)	Initial concentration remaining (%) (Mean \pm SD)		
	23 \pm 2 °C		8 \pm 1 °C
	Exposed to light		Protected from light
0	100.00	100.00	100.00
3	94.77 \pm 0.6	96.20 \pm 2.1	98.99 \pm 0.3
5	93.64 \pm 1.4	94.79 \pm 0.8	98.75 \pm 1.2
7	93.26 \pm 2.1	93.20 \pm 1.8	96.99 \pm 1.4
10	91.87 \pm 0.3	92.88 \pm 2.0	94.75 \pm 2.1
15	90.69 \pm 1.7	91.71 \pm 0.5	92.53 \pm 0.8

Table 5. Stability of injectable haloperidol

3.1.3 Method for L-DOPA tablets

For the quantification of L-DOPA in tablets, the method was linear between 100 ng/band to 500 ng/ band ($r = 0.999$). The intra-assay variation was between 0.26% and 0.65% and the inter-assay was between 0.52% and 2.04%. LOD was 1.12 ng, and LOQ was 3.29 ng. The accuracy ranged from 100.40 % to 101.09%, with a coefficient of variation not higher than 1.40%. The method was selective for L-DOPA ($R_f = 0.37$) and carbidope ($R_f = 0.79$) (Fig. 12).

Table 6 shown the values for the precision study of the method.

The values found for the accuracy of the method can be observed at Table 7.

At Table 8 can be observed the values found for the determination of L-DOPA in tablets by the proposed HPTLC method and by the USP HPLC method.

Accelerated stability study was performed on commercial tablets of L-DOPA. The temperature used was 40 ± 2 °C and the relative humidity was 75 ± 5 (Zone II, OMS). The study was carried out by three months, taking samples to $t=0$ and one time each month.

Concentration (ng/ μ L)	Relative standard deviation (RSD), %		
	Instrumental precision ^a	Intraassay precision ^b	Intermediate precision ^c
100	0.45	0.48	2.04
300	0.68	0.65	0.77
500	0.23	0.26	0.52

^a n= 10; analyzed on the same day; ^b n= 5; analyzed on the same day (for each concentration)

^c n= 9; analyzed on three different days (for each concentration)

Table 6. Precision of the method

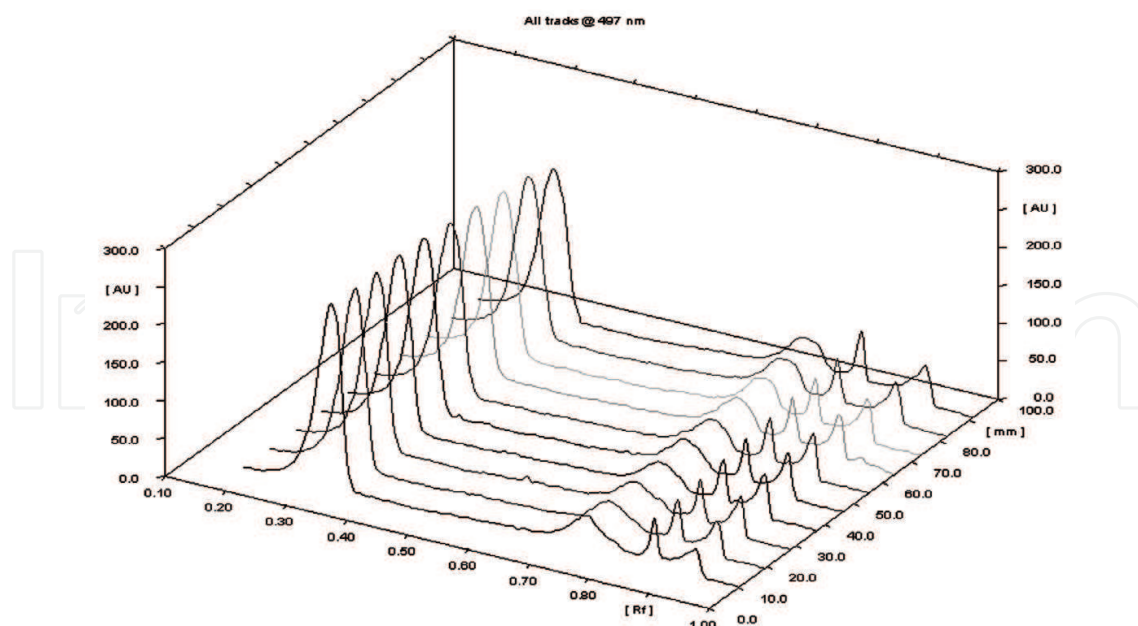


Fig. 12. Selectivity of the method. Peak 1 (from left to right): L-DOPA; peak 2: Carbidope (dopa-decarboxilase inhibitor)

Added concentration (ng/ μ L)	Found concentration (ng/ μ L) ^a	Accuracy, % ^b	RSD, %
Intraassay (n=9)			
320	322.10 \pm 4.20	100.66	1.30
400	404.22 \pm 3.70	101.06	0.92
480	485.25 \pm 1.20	101.09	0.25
Interassay (n=27)			
320	321.27 \pm 4.50	100.40	1.40
400	402.30 \pm 3.80	100.58	0.94
480	482.83 \pm 2.35	100.60	0.49

^a Each value is the mean \pm standard deviation; ^b (Found concentration/ added concentration) \times 100.

Table 7. Method accuracy

Parameter	HPTLC	HPLC
Labelled claim (mg per tablet)	100.00	100.00
Amount found ^a (mg per tablet)	90.99	90.00
RSD (%)	2.40	1.53

F calc.: 11.86; F theoretical^b: 13.61

^a Each result is the mean of nine experiments (three solutions, three determinations of each of them).

^b $\alpha = 0.05$

Table 8. Comparison for determination of L-DOPA in tablets by the proposed method and by HPLC

Tablets were processed as follow (USP, 2007): 20 tablets were weighed and ground into fine powder and an accurately weighed portion equivalent to 30 mg of L-DOPA was diluted to 100 mL with water: methanol (7:3, v/v). The solution was centrifuged and then, 1 mL of the supernatant was diluted to a 10 mL with the mixture solvent.

Results of the accelerated stability study can be observed at Table 9.

t(months)	Percentage L-DOPA per tablet	Quantity L-DOPA per tablet (mg)
0	100.00	90.99
1	96.65	87.94
2	87.21	79.35
3	85.60	77.89

Table 9. Results for the accelerated stability study of L-DOPA tablets

Therefore, at the second month of accelerated stability study, L-DOPA tablets don't have a change significant at the percentage of active principle per tablet, but at the third month of the study, the change at the percentage is more than a 5% (ICH, 2003).

4. Conclusion

The proposed HPTLC methods are a new analytical alternative for quantification of the mentioned drugs in these dosage forms. None HPTLC method for quantitative analysis of fluphenazine hydrochloride in injections, haloperidol in injections and L-DOPA in tablets were found in literature before our methods.

These methods are simple, fast, precise, sensitive (low LOD and LOQ values), accurate and specific for the quantification of these drugs in the dosage forms studied. Moreover, HPTLC allows for a large number of samples to be measured simultaneously, very important, especially in quality control.

The procedure works without separation steps, only centrifugation, because the excipients are not dissolved by the working solvents.

Therefore, the proposed HPTLC methods are very good methods for quantitative analysis of fluphenazine hydrochloride in injection, haloperidol lactate in injections, and L-DOPA in tablets, being appropriate to stability studies.

By the other side, the results indicate that haloperidol lactate injection (glass ampoules) could be stored for at least 15 days and use when needed, reducing wastage and unnecessary expenses. This could result in substantial money savings for some institutions.

5. Acknowledgment

The authors would like to thank the Research Council at the University of Concepción (Project DIUC 201.074.034-1.0 and Project DIUC 204.074.034-1.0), and to Pharmacists Miss Loreto Pino, Mr. Mario Nail, Mr. Jonathan Contreras and Mr. Cristobal Reyes.

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Quality Control of Herbal Medicines and Related Areas

Edited by Prof. Yukihiko Shoyama

ISBN 978-953-307-682-9

Hard cover, 282 pages

Publisher InTech

Published online 07, July, 2011

Published in print edition July, 2011

The authors of this thematic issue provide a comprehensive summary of most recent knowledge and references on quality control in wide fields. Quality control is essential for natural products like natural medicine and related food products. In this issue fifteen chapters have been included, discussing in detail various aspects of quality control. It will certainly prove useful not only for phytochemical researchers, but also many scientists working in numerous fields. Much effort has been invested by the contributors to share current information. Without their efforts and input 'Quality Control of Herbal Medicine and Related Areas' could not exist.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Sigrid Mennickent, Marta de Diego, Mario Vega and Carmen Gloria Godoy (2011). Quantitative Determination of Drugs in Dosage Forms as a Tool of Quality Control Studies, Quality Control of Herbal Medicines and Related Areas, Prof. Yukihiko Shoyama (Ed.), ISBN: 978-953-307-682-9, InTech, Available from: <http://www.intechopen.com/books/quality-control-of-herbal-medicines-and-related-areas/quantitative-determination-of-drugs-in-dosage-forms-as-a-tool-of-quality-control-studies>

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