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Simultaneous Determination of Paracetamol, Domperidone and Flunarizine in Combined Tablet Dosage Form Using RP-HPLC Method

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A simple, selective, accurate high performance liquid chromatographic (HPLC) method have been developed and validated for the analysis of paracetamol, domperidone and flunarizine. Chromatographic separation was achieved on Luna C_8 column using mobile phase of methanol:acetonitrile:phosphate buffer (55:30:15, % v/v/v, pH 7.0) at a flow rate of 1.0 mL/min with UV detection at λ_{max} of 249, 284 and 254 nm for paracetamol, domperidone and flunarizine, respectively. The retention time of paracetamol, domperidone and flunarizine was found to be 2.95, 4.05 and 10.3 min, respectively. The method was validated as per ICH guidelines. The method may be applied for the routine simultaneous estimation of the above mentioned drugs in tablet dosage form.

Key Words: RP-HPLC, Paracetamol, Domperidone, Flunarizine.

INTRODUCTION

Paracetamol ($C_0H_9NO_2$) is chemically 4-hydroxyacetanilide[1] and contains analgesic and antipyretic properties[2]. Domperidone ($C_{22}H_{24}ClN_5O_2$ is chemically 5-chloro-1-1*H*-[3-(2,3-dihydro-2-oxo-1*H*-benzimidazol-1-yl)propyl]-4-piperidinyl-1,3-dihydro-2*H*-benzimidazol-2-one). It is antiemetic[3]. Flunarizine ($C_{26}H_{26}N_2F_2$) is chemically 1-[*bis*(4-fluorophenyl)methyl]-4-(3-phenyl-2-propenyl)piperazine[4]. The structures of the drugs are shown in Fig. 1. Many methods have been reported in the literature for the estimation of paracetamol, domperidone and flunarizine alone or in combination with other drugs. However there is no RP-HPLC method reported for the simultaneous estimation of these drugs in combined dosage forms. Fixed dose combination containing paracetamol (500 mg), domperidone (10 mg) and flunarizine (5 mg) available in the tablet form in the market. This paper describes a novel method for the simultaneous estimation of paracetamol, domperidone and flunarizine tablets dosage form. The procedure based on the use of reversed phase-high performance liquid chromatography, is simple rapid and provides accurate and precise results. The proposed methods were optimized and validated according to current International Conference on Harmonization (ICH) guidelines[5].

EXPERIMENTAL

Gratis sample of paracetamol, domperidone was received from schon Pharmaceutical Pvt. Ltd. (Indore). Flunarizine was

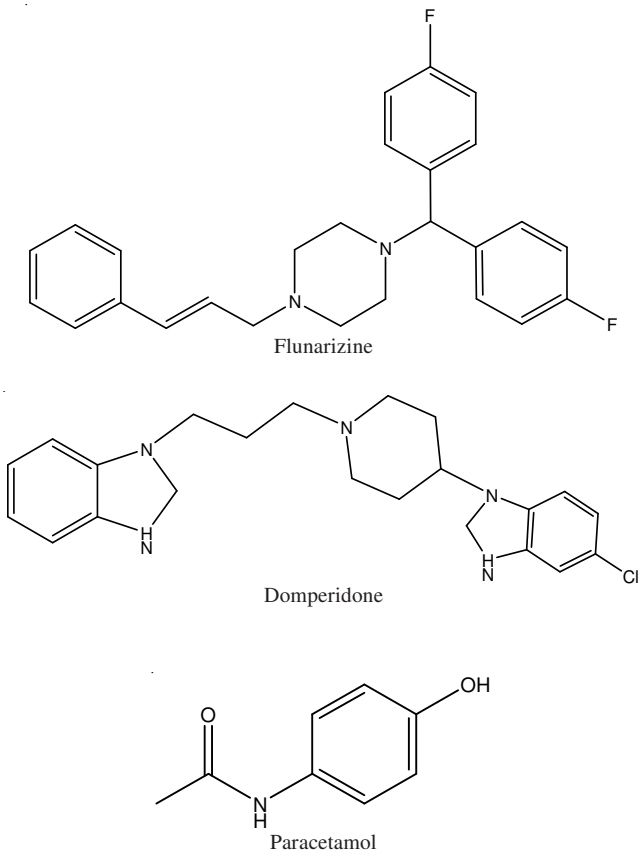

Fig. 1. Chemical structures of flunarizine, domperidone and paracetamol

received from Solitaire Pharmacia Pvt. Ltd. (Chandigarh). All the chemicals used were HPLC-grade and was purchased from Merck Ltd. Mumbai, (India). The percentage purity of paracetamol, domperidone and flunarizine were found to be 99.79, 99.59 and 99.0 %, respectively.

Chromatographic condition: The LC system consisted of LC $10AT_{VP}$ (Make; Shimadzu, Japan) gradient pump with universal loop injector (Rheodyne 7725i) of 20 µL injection capacity, photodiode array detector (PDA) SPD-10 A_{VP} and Phenomenex Luna C_8 (25 cm × 5 µm × 4.6 mm i.d.) column, controlled by a PC work station equipped with software CLASS-Vp (software M-10, version 1.6).

The mobile phase was composed of methanol, acetonitrile, and phosphate buffer in the ratio of (55:30:15, % v/v/v, pH 7.0). Flow rate was kept at 1.0 mL/min elution was monitored at λ_{max} of 249, 284 and 254 nm for paracetamol, domperidone and flunarizine, respectively. Peak area was used to prepare calibration curve against their respective concentration.

Standard stock solutions: The equivalent of 10 mg each of paracetamol, domperidone and flunarizine were accurately weighed in a 10 mL volumetric flask and dissolved in the mobile phase and filled up to volume with the mobile phase. These standard stock solutions were observed to contain 1000 µg/mL for paracetamol, domperidone and flunarizine. From the standard stock solutions of 1000 µg/mL and different dilutions were prepared for each drug having concentration from 10, 20, 30, 40 and 50 µg/mL with mobile phase. 20 µL of these solutions were injected into the LC system with the help of Hamilton syringe.

Analysis of tablets: As the results of mixed standard analysis were found satisfactory, the method was applied for the quantitative study of all the two drugs in commercially available tablet. 20 tablet of migrest were weighed and powder equivalent to 10 mg of domperidone was taken in 100 mL volumetric flask and dissolved in 10 mL of mobile phase methanol:acetonitrile:phosphate buffer (55:30:15 %v/v/v/, pH 7.0) with vigorous shaking for 5-10 min. The supernatant liquid was transferred to 100 mL of volumetric flask through a whatman # 45 filter paper. The residue was washed twice with solvent and the combined filtrate was suitably diluted. Five replicates of sample solutions were prepared and 20 µL of each replicates were injected. The concentrations of these drugs were extrapolated from their respective calibration curves by using the area[6-8].

Recovery study: To check the accuracy of the developed method recovery study was carried out is triplicate as per ICH guideline. Standard solutions of all the three drugs were added equivalent to 80, 100 and 120 % of target drug concentration. Precision of the method was checked using three replicates over three concentration levels of within range expressed as % RSD values.

RESULTS AND DISCUSSION

For the RP-HPLC method, chromatographic conditions were optimized to achieve the best resolution and peak shape for paracetamol, domperidone and flunarizine Mobile phase consist methanol:acetonitrile:phosphate buffer (55:30:15, % v/v/v, pH 7.0) was selected as optimal for obtaining well-defined and resolved peaks. The quantitation was carried out at λ_{max} of 249, 284 and 254 nm for paracetamol, domperidone and flunarizine (Fig. 2). Table-1 summarizes linearity range, limit of detection (LOD), limit of quantitation (LOQ) and system suitability parameters for the RP-HPLC method. The proposed method was used to conduct assay of commercially available tablets containing paracetamol, domperidone and flunarizine (Table-2). Three replicate determinations were performed on the accurately weighed amounts of tablets. Linearity range were found to be in the range of 10-150, 8-90 and 7-100 µg/mL with LOQ of 0.2, 0.2 and 0.09 for paracetamol, domperidone and flunarizine, respectively, the recovery study showed an acceptable range of variation below RSD of 2. The solution was found to be stable in precision study for long period of time.

TABLE-1
VALIDATION AND SYSTEM SUITABILITY PARAMETERS FOR RP-HPLC METHOD

Parameters	PCM	DOM	FLZ
Linearity range(µg/mL)	10-150	8-90	7-100
λ_{max} (nm)	249	284	254
Limit of detection(µg/mL)	0.09	0.08	0.03
Limit of quantitation(µg/mL)	0.2	0.2	0.09
Theoretical platenumber	3001	4342	11723
Retention time(min)	2.97	3.89	9.85
Tailing factor	1.5	1.3	1.1
Capacity factor(k')	–	2.88	3.74
Resolution	–	4.05	20.00

PCM = Paracetamol, DOM = Domperidone, FLZ = Flunarizine

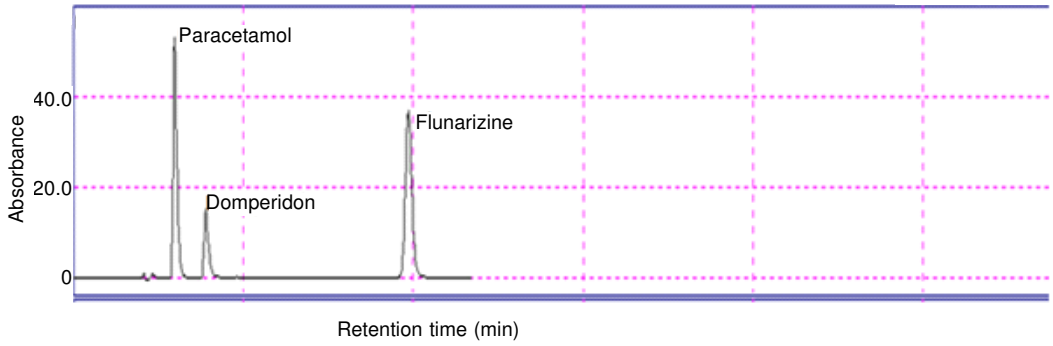

Fig. 2. Chromatograms of 55 µg/mL PCM, 10 µg/mL DOM and 10 µg/mL FLZ at λ_{max} of 249, 284 and 254 nm, respectively in methanol:acetonitrile:phosphate buffer (pH 7.0) (55:30:15 % v/v/v) as mobile phase

TABLE-2
RESULTS OF COMMERCIAL TABLET ANALYSIS AND STATISTICAL VALIDATION OF RECOVERY STUDY

Particulars	Conc. of drug added(%)	PCM conc. found(%)†	DOM conc. found(%)†	FLZ conc. found(%)†
Recovery study	80	100.01± 1.95	100.2±1.34	101.46 ± 2.89
	100	101.08 ± 1.64	101.51 ± 2.12	100.7.9 ± 2.23
	120	99.21 ± 2.29	101.3 ± 1.38	101.5 ± 1.69
Commercial tablet analysis		100.2±1.3[a]	104±1.4[a]	103.6±2.0[a]

†55µg/mL for PCM, 10µg/mL for DOM and 10 µg/mL for FLZ, respectively(RSD %, n= 5). [a]Mean ±RSD (n=3); PMC = paracetamol, DOM = domperidone, FLZ = flunarizine

Conclusion

The validated RP-HPLC method developed here proved to be simple, fast, accurate, precise, and sensitive. The developed method was validated as per ICH guidelines[5]. Thus it may be used for routine analysis of paracetamol, domperidone and flunarizine in combined tablet dosage form.

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