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Research Article

Development and Validation of New Analytical Methods for the Quantification of Prucalopride Succinate

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Abstract

Prucalopride succinate is used for the treatment of chronic constipation. Four new UV spectrophotometric methods have been developed for the determination of Prucalopride succinate in pharmaceutical formulations. Prucalopride succinate is a selective, high affinity 5-HT4 receptor agonist which targets the impaired motility associated with chronic constipation and thus normalizing bowel movements. Prucalopride succinate has shown absorption maxima (λmax) at 226 nm in reagents phosphate buffer (pH 2.0), 0.1N HCl and Beer-Lambert's law was obeyed over the concentration range 5 - 60 µg/ml. Prucalopride succinate has also shown λmax at 222.60 nm and 228 nm in 0.1N NaOH and acetate buffer (pH 5.0) respectively and Beer-Lambert's law was obeyed over the concentration range 5 - 50 µg/ml. All the four methods were validated as per ICH guidelines and the methods were found to be simple, precise and accurate and can be applied successfully for the assay of Prucalopride succinate for the pharmaceutical formulations.

Keywords: Prucalopride Succinate; Spectroscopy; Phosphate Buffer; Acetate Buffer; Sodium Hydroxide; HCl; Validation

Introduction

Prucalopride succinate (Figure 1), a first in class dihydro-benzofuran-carboxamide, is a selective, high affinity serotonin (5-HT_4) receptor agonist with enterokinetic activities. Prucalopride alters colonic motility patterns via serotonin 5-HT_4 receptor stimulation: it stimulates colonic mass movements, which provide the main propulsive force for defecation. Prucalopride succinate ($C_{22}H_{32}ClN_3O_7$; Mol. Wt. 485.96 g/mol) is chemically 4-amino-5-chloro-2,3-dihydro-N-[1-(3-methoxy propyl)-4-piperidinyl]-7-benzo furan carboxamide butanedioic acid. Various analytical methods have been developed for the determination of Prucalopride succinate in the literature. Buiter., *et al*. evaluated the preclinical evaluation of [11C] prucalopride as a potential agonist PET ligand for the 5-HT_4 receptor using radiosynthesis [2]. Virag., *et al*. established HPLC [3], Sun Z., *et al*. UHPLC-MS/MS method in rat plasma [4] for the quantitation of prucalopride and Mahamuni., *et al*. separated and characterised the stress degradation products and process impurities of Prucalopride by LC-QTOF-MS/MS [5]. At present four new UV spectrophotometric methods have been proposed for the determination of Prucalopride succinate in pharmaceutical formulations and the method was validated [6].

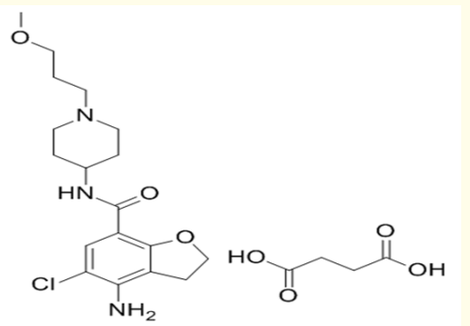

Figure 1: Chemical structure of prucalopride succinate.

Materials and Methods

Double beam spectrophotometer (SHIMADZU Model No. UV - 1800) with quartz cells was used for the present study. All the solutions were scanned at 200 - 400 nm range. Prucalopride succinate is available as film coated tablets (2 mg) with brand name RESOLOR (2 mg) (Shire Biotech India Pvt Ltd) and PRUEASE™ (SUN Pharma), PRUCAPLA (Cipla). Prucalopride succinate was obtained as a gift sample from SYMED LABS Ltd (India). Reagents such as 0.1N HCl (Method I), phosphate buffer (pH 2.0) (Method II), acetate buffer (pH 5.0) (Method III) and 0.1N NaOH (Method IV) were prepared as per IP 2010.

Procedure

25 mg of Prucalopride succinate was accurately weighed and transferred in to a 25 ml volumetric flask and dissolved in methanol (1000 µg/ml) (Stock solution) and a series of dilutions were prepared with 0.1N HCl, phosphate buffer (pH 2.0), acetate buffer (pH 5.0) and 0.1N NaOH for Method I, II, III and IV respectively as per the requirement.

Method validation

Linearity

A series of Prucalopride succinate solutions (5 - 60 µg/ml) were prepared using 0.1N HCl (Method I), phosphate buffer pH 2 (Method II) and (5 - 50 µg/ml) using acetate buffer pH 5.0 (Method III) and NaOH (Method IV) and scanned (200 - 400 nm) against their

reagent blank. Prucalopride succinate has shown λ_{max} at 226 nm in reagents phosphate buffer (pH 2.0), 0.1N HCl and λ_{max} at 222.60 nm and 228 nm in 0.1N NaOH and acetate buffer (pH 5.0) respectively. The absorbance of these solutions in their solutions were recorded at their λ_{max} for Method I, II, III and IV and calibration curves were drawn by taking the concentration on the X-axis and the corresponding absorbance on the Y-axis for all the methods.

Precision and accuracy

Precision was studied by measuring the absorbance of 6 solutions of the same concentration (n = 6) and there by mean, standard deviation and relative standard deviation were calculated. Accuracy was studied by spiking the formulation solution of a fixed concentration with pure drug solution (50%, 100% and 150%) by standard addition method and there by percentage recovery and relative standard deviation were calculated.

Assay of prucalopride succinate tablets

20 tablets of Prucalopride succinate of two different brands were procured from the local pharmacy store and tablet powder consisting of 25 mg of Prucalopride succinate was accurately weighed and extracted with methanol. The contents were sonicated well, filtered and dilutions were made with respective buffers for Method I, II, III and IV and assay was performed.

Results and Discussion

Prucalopride succinate is a selective, high affinity 5-HT_4 receptor agonist which targets the impaired motility associated with chronic constipation and thus normalizing bowel movements. Four new UV spectrophotometric methods were developed for the determination of Prucalopride succinate in reagents 0.1N HCl (Method I), phosphate buffer (pH 2.0) (Method II), acetate buffer (pH 5.0) (Method III) and 0.1 N NaOH (Method IV). Table 1 shows the previously published methods in the literature and the present proposed methods were compared with them. Prucalopride succinate has shown absorption maxima (λ_{max}) at 226 nm in reagents 0.1N HCl, phosphate buffer (pH 2.0) and 222.60 nm as well as 228 nm in 0.1N NaOH and acetate buffer (pH 5.0) respectively. Beer-Lambert's law was obeyed over the concentration range 5 - 60 µg/ml for Method I and Method II and the linearity range for Method III Method IV was 5 - 50 µg/ml. The absorption spectra obtained for all the four methods was shown in figure 2 and the calibration curves were shown in figure 3.

Method	Mobile Phase/Reagents	Λ (nm)	Linearity (µg/mL)	Ref
RP-HPLC	10 mM potassium dihydrogen phosphate buffer (pH 2.0): methanol (50:50)	225	50 - 150	3
UHPLC-MS/MS	acetonitrile-water (containing 0.1% formic acid)	-	0.1 - 100 x 10^{-3} ng/mL	4 Rat Plasma
LC-QTOF-MS/MS	20 mM ammonium bicarbonate buffer and acetonitrile: methanol (80:20 v/v)	-	-	5 Impurities
Spectrophotometry	HCl Phosphate buffer Acetate buffer NaOH		5 - 60 5 - 60 5 - 50 5 - 50	Present methods

Table 1: Literature review of prucalopride succinate.

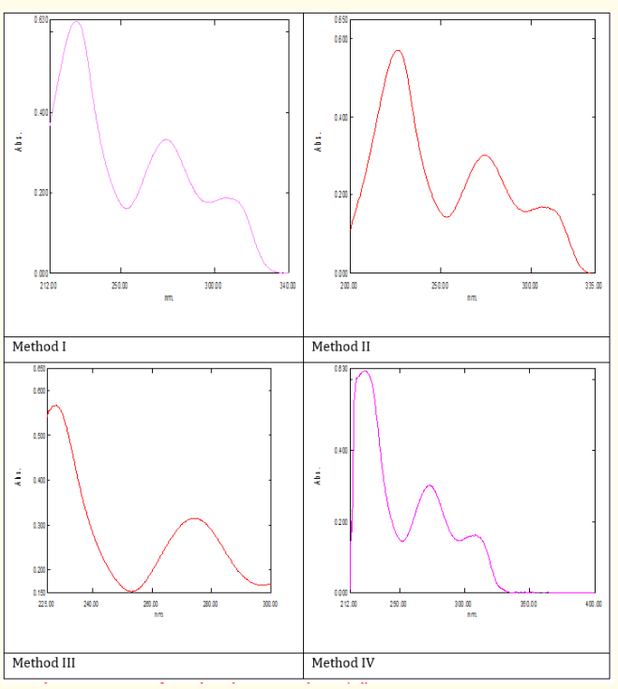

Figure 2: Absorption spectra of prucalopride succinate (10 µg/ml).

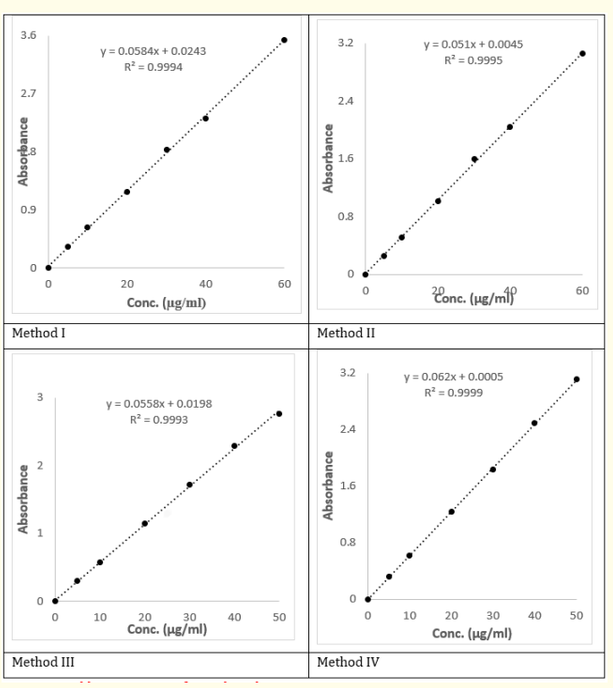

Figure 3: Calibration curves of prucalopride succinate.

Conc. (µg/ml)	Absorbance			
	Method I	Method II	Method III	Method IV
5	0.3243	0.2543	0.32	0.304
10	0.6256	0.5086	0.623	0.568
20	1.1732	1.01	1.24	1.145
30	1.8298	1.592	1.823	1.717
40	2.3201	2.034	2.49	2.29
50	-	-	3.11	2.762
60	3.527	3.0516	-	-

Table 2: Linearity of prucalopride succinate.

Parameters		Method I	Method II	Method III	Method IV
Reagent		0.1 N HCl	Phosphate buffer	Acetate buffer	0.1 N NaOH
Linearity (µg/ml)		5 - 60	5 - 60	5 - 50	5 - 50
λ_{max} (nm)		226	226	222.60	228
Molar extinction coefficient (litre/mole/cm^{-1})		3.0404×10^4	2.4717×10^4	2.8479×10^4	3.0277×10^4
Sandell's sensitivity (µg/cm^2/0.001 absorbance unit)		0.015	0.019	0.017	0.016
Slope		0.0584	0.051	0.0558	0.062
Intercept		0.0243	0.0045	0.0198	0.0005
Correlation coefficient		0.9994	0.9995	0.9993	0.9999
Precision (%RSD)	Intraday	0.82 - 0.93	0.824 - 0.97	0.79 - 0.96	0.76 - 0.92
	Interday	0.97 - 1.01	0.91 - 1.05	0.84 - 0.99	0.79 - 1.05
Accuracy (% RSD)		0.93 - 1.00	0.93 - 0.97	0.82 - 0.97	0.84 - 0.91

Table 3: Optical characteristics of Prucalopride succinate.

Brand	Method I		Method II		Method III		Method IV	
	Observed amount (mg)	% Recovery	Observed amount (mg)	% Recovery	Observed amount (mg)	% Recovery	Observed amount (mg)	% Recovery
I	1.99	99.5	1.96	98	1.98	99.0	1.97	98.5
II	1.97	98.5	1.93	96.5	1.97	98.5	1.98	99.0

Table 4: Assay of prucalopride succinate (Label claim: 2 mg).

*Mean of three replicates.

Conclusion

The new proposed spectrophotometric methods were validated and applied for the pharmaceutical formulations i.e. tablets. The proposed methods are simple, precise, accurate, economical and the methods can be successfully applied for the determination of Prucalopride succinate in pharmaceutical dosage forms.

Acknowledgment

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