

## Determination of strontium ranelate in pure and pharmaceutical formulations by oxidimetry

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### ABSTRACT

Two simple and sensitive spectrophotometric methods A, B have been developed for the estimation of Strontium Ranelate. The method A is based on oxidation of the drug with oxidant Potassium permanganate followed by the estimation of unreacted oxidant with Fast green FCF. Method B involves the addition of excess CAT of a known concentration in the presence of 0.25M HCl and determining the unreacted CAT by measuring the absorbance of the Dye Gallo cyanine. The absorption maxima were found to be at ( $\lambda_{\max}$  630nm for A, 540 nm for B). These methods obey Beer's law limits (2-10 $\mu\text{g ml}^{-1}$  for A), (2-10 $\mu\text{g ml}^{-1}$  for B) and give reproducible results. The percentage recoveries are 99.89 $\pm$ 0.37 to 100.31 $\pm$ 0.59 (for A), 99.55 $\pm$ 0.77 to 100.32 $\pm$ 0.44 (for B) respectively. © 2013 Trade Science Inc. - INDIA

### KEYWORDS

Strontium ranelate (SRN);  
Gallo cyanine (GC);  
Chloramine-T (CAT);  
Fast green FCF (FGFCF);  
Potassium permanganate.

### INTRODUCTION

Strontium Ranelate (SRN) is chemically known as Distrontium 5 - [bis (2-oxido-2 oxoethyl) amino]-4-cyano-3-(2-oxido-2-oxoethyl) thiophene-2-carboxylate (Figure 1). It is official in<sup>[1-6]</sup>. The active functional groups present in SRN are Carboxyl and its strontium salt, tertiary amine, substituted thiophene. SRN is the only anti osteoporotic agent which both increases bone formation and reduces bone resorption, resulting in a rebalance of bone turnover in favor of bone formation. Strontium ranelate stimulates the calcium sensing receptors and leads to the differentiation of pre-osteoblast to osteoblast which increases the bone formation. Strontium ranelate also stimulates osteoblasts to secrete osteoprotegerin in inhibiting osteoclasts formed from

pre-osteoclasts in relation to the RANKL system, which leads to the decrease of bone resorption. Strontium ranelate is unusual in that the cation (strontium) is responsible for the pharmacological effect, whereas in most modern medications it is the base (anion) that is the active ingredient. In early scientific pharmacology, cations such as arsenic, bismuth, mercury and lithium

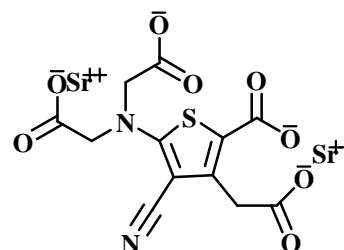


Figure 1: Chemical structure of Strontium Ranelate

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were frequently used but recently anions have been much more in vogue. A very few physio-chemical methods appeared in the literature for the determination of SRN in pharmaceutical formulations (less) and more for the plasma samples. The methods so far reported includes HPLC<sup>[7,8]</sup>, AAS<sup>[9]</sup> spectrophotometric<sup>[10,11]</sup>. The analytically important functional groups of SRN were not properly exploited designing suitable spectrophotometric methods for the determination of the selected drug. In the present paper, we describe two visible spectrophotometric methods based on reaction of the selected drug with Permanganate (Method-A), the un reacted permanganate was then determined by FGFCF<sup>[12-14]</sup>. In the method (B), CAT undergoes hydrolysis in aqueous acid medium to give sodium hypochlorite followed by Hypo chlorous acid. This reacts with SRN to form the relevant oxidant products, probably a mixture which appears to be reproducible under the specified experimental conditions. The remaining Hypochlorous acid may be responsible for the bleaching of the colour GC through destruction of the extended chromophoric system, by excess of CAT and the un reacted CAT oxidizes the Oxazine Dye, Gallocyanine to a colorless form there by causing a decrease in the absorbance of GC<sup>[15-17]</sup>.

## EXPERIMENTAL

AUV-1601, and SHIMADZU digital spectrophotometer with 1cm matched quartz cells were used for the spectral and absorbance measurements. A SYSTRONICS digital pH meter 361 was used for pH measurements. All the chemicals and reagents were of analytical grade and the solutions were prepared freshly. Aqueous solutions of  $\text{KMnO}_4$  solution (BDH, 0.03%,  $1.89 \times 10^{-3}$  M), FG FCF solution (Chroma, 0.01%,  $1.236 \times 10^{-4}$  M) Solution for Method-A,  $\text{Na}_2\text{SO}_4$  solution (BDH, 14.2%, 1.0M), CAT solution (Loba, 0.02%,  $7.10 \times 10^{-4}$  M), GC solution (Chroma, 0.01%,  $2.969 \times 10^{-4}$  M) for Method-B respectively in tripple distilled water.

### Standard drug solutions

A 1mg/ml solution was prepared by dissolving 100mg of pure SRN in 100ml of water and further diluted to 50-250g/ml for both methods.

## Recommended procedures

### (a) Method A

Into a series of 25 ml calibrated tubes containing aliquots of standard SRN solution (0.5- 2.5 ml, 100  $\mu\text{g/ml}$ ), 0.5ml of  $\text{KMnO}_4$  solution was added and the total volume in each tube was brought to 5.0 ml with distilled water and kept aside for 10 min at lab temperature. Then 4.0 ml each of FGFCF solution and sodium sulphate solution were added successively and kept aside for 5 min. The volume was made up to the mark with distilled water. The absorbance was measured at 630 nm (Figure 2) against distilled water. The blank (omitting drug) and dye (omitting drug and oxidant) solutions were prepared in a similar manner and their absorbances were measured against distilled water. The decrease in absorbance corresponding to consumed permanganate and in turn the drug concentration was obtained by subtracting the decrease in absorbance of test solution (dye-test) from that of the blank solution (dye-blank). The amount of SRN present was

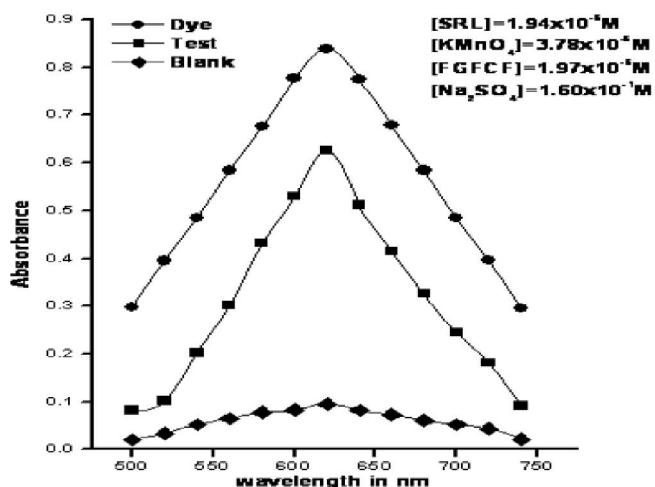


Figure 2 : Absorption spectrum of SRN with  $\text{MnO}_4^-/\text{FGFCF}$

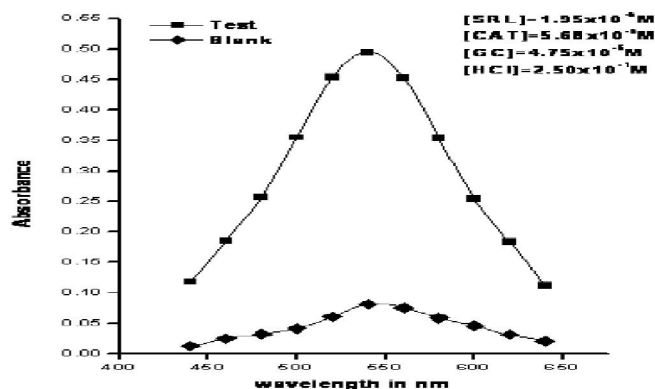


Figure 3 : Absorption spectrum of SRN with GC/CAT

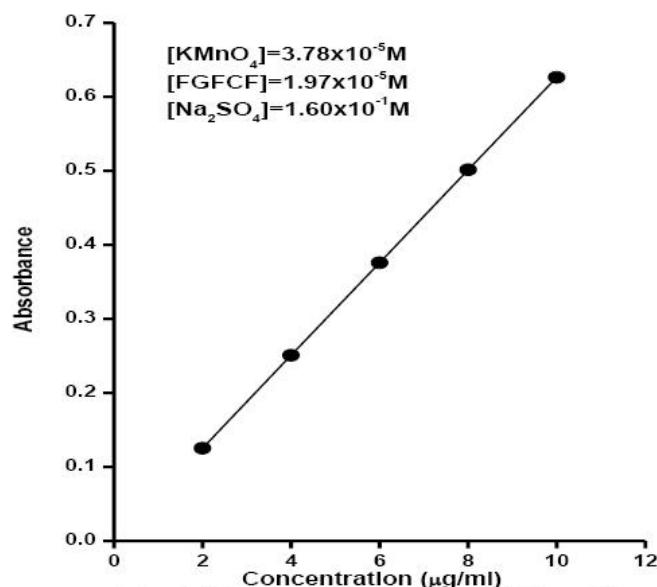


Figure 4 : Beer.s plot of SRN with MnO<sub>4</sub>/FGFCF system

calculated from its Beer.s plot (Figure 4).

### (b) Method B

To each of 25 ml graduated tubes containing standard SRN solution (0.5 -2.5 ml, 100 µg/ml), 1.25 ml of 5M HCl and 2.0 ml of 0.02% CAT were added and the solution was diluted to 20 ml with distilled water. After 10 min, 4 ml of GC (0.01%) solution was added, mixed thoroughly and the volume was made upto the mark with distilled water. The absorbances were measured after 15 min at 540 nm (Figure 3.) against a reagent blank. A blank was carried out in a similar manner. The decrease in absorbance corresponding to consumed CAT, which in turn to the drug quantity was obtained by subtracting the absorbance of the blank solution from that of the test solution. The calibration graph was drawn by plotting the decrease in the absorbance of the dye (GC), against amount of the drug. Amount of the drug in any sample was computed from its Beer.s plot (Figure 5).

## RESULTS AND DISCUSSION

In developing these methods, a systematic study of the effects of various relevant parameters in the concerned were undertaken by varying one parameter at a time and controlling all other parameters to get maximum colour development, minimum blank colour, reproducibility and reasonable period of stability of final coloured species formed. The conditions so obtained

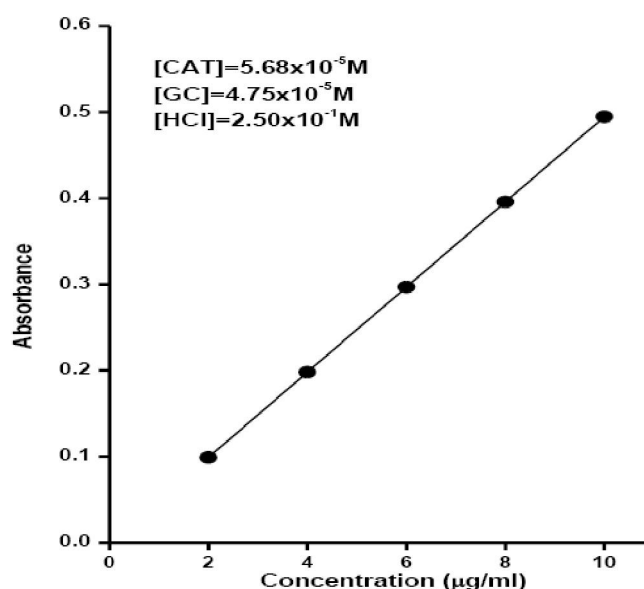


Figure 5 : Beer.s plot of SRN with GC/CAT system

TABLE 1 : Optical characteristics, precision, accuracy of the methods proposed in the determination of SRN

S.No	OPTICAL CHARACTERISTICS	Method-A	Method-B
1	$\lambda_{\max}$ (nm)	630	540
2	Beer's Law limits(µg/ml)	2-10	2-10
3	Molarabsorptivity(l mol <sup>-1</sup> cm <sup>-1</sup> )	3.21x10 <sup>4</sup>	2.53x10 <sup>4</sup>
4	Correlation coefficient (r)	0.9999	0.9998
5	Sandell's sensitivity (µg/cm <sup>2</sup> /0.001 absorbance unit)	0.01596	0.0202
6	Regression equation(y=a+bc)(i)slope (b)	0.062	0.049
	(ii) Standard deviation on intercept(S <sub>b</sub> )	9.05x10 <sup>-4</sup>	6.24x10 <sup>-4</sup>
	(iii)intercept (a)	0.00006	0.00008
	(iv) standard deviation (S <sub>a</sub> )	6.00x10 <sup>-3</sup>	4.14x10 <sup>-3</sup>
	(v)Standard error of estimation(S <sub>c</sub> )	5.72x10 <sup>-3</sup>	3.94x10 <sup>-3</sup>
7	Optimum photometric range (µg/ml)	4.36-12.58	4.46-10
8	Relative Standard deviation *	0.29	0.47
9	Detection limit	0.305	0.494
10	% of range of error(confidence limit)	0.478	0.775
	(i)0.05 level		
	(ii)0.01 level	0.281	0.241

were incorporated in the recommended procedures. The optical characteristics such as Beer.s limits, molar

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absorptivity, and sandell.s sensitivity are given in TABLE 1. Regression analysis using the method of least Squares was made to evaluate the slope (b), intercept (a), and correlation Co-efficient (r) for each system are presented in TABLE 1. The accuracy of the methods was ascertained by comparing the results obtained for pharmaceutical formulations by the proposed methods and

reference method by UV, developed in the laboratory using drug solutions, Statically by the t-and f-tests and the results are summarized TABLE 2. Recoveries were determined by adding standard drug to the pre analysed pharmaceutical formulations. The ingredients usually present in pharmaceutical formulations did not interfere in the proposed methods.

TABLE 2 : Determination of srn in pharmaceutical formulations

Method	Pharmaceutical Formulations	Labeled Amount (mg)	Proposed Methods			Found by Reference method± S.D.	% Recovery by proposed methods** ±S.D.
			Amount found*(mg) ± S.D.	F	t		
A	SACHET-I	2	2.03±0.30	1.00	1.08	1.98±0.30	99.89±0.37
	GRANULES-II	2	2.04±0.21	1.36	1.82	1.99±0.18	99.96±0.76
	SACHET - III	2	1.96±0.31	1.42	0.84	1.97±0.26	100.01±0.53
	GRANULES-IV	2	2.02±0.22	1.67	1.00	2.03±0.17	100.31±0.59
B	SACHET – I	2	1.98±0.30	1.00	1.15	1.98±0.30	99.61±0.33
	GRANULES-II	2	1.98±0.13	1.91	1.06	1.99±0.18	99.55±0.77
	SACHET-III	2	1.98±0.30	1.33	1.00	1.97±0.26	100.16±0.49
	GRANULES-IV	2	1.97±0.22	1.67	1.00	2.03±0.17	100.32±0.44

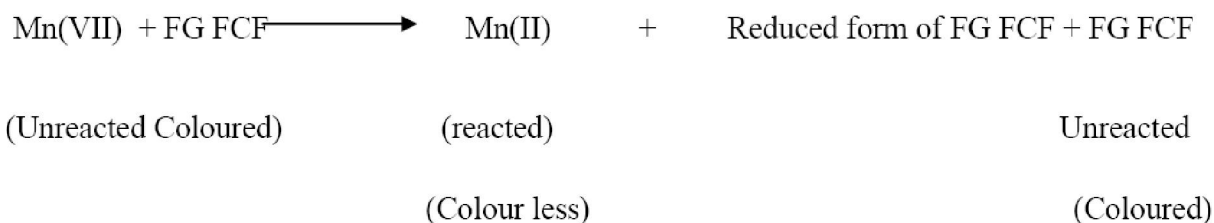
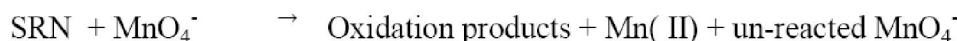
\* Average ± standard deviation of eight determinations, the t and F – values refer to comparison of the proposed method with reference method. Theoretical values at 95% confidence limits t = 2.365 and F = 4.88; \*\* Average of five determinations.

### Colored species formation

#### (a) Method A

SRN exhibits reducing property due to the presence of functional moieties (one or more) vulnerable to oxidation selectively with oxidizing agents such as  $\text{KMnO}_4$  or CAT under controlled experimental conditions. When treated with known excess of oxidant, SRL undergoes oxidation, giving products of oxidation besides un reacted oxidant. It is possible to estimate the

drug content colourimetrically, which is equivalent to either the reacted oxidant or reduced form of oxidant formed. The un-reacted oxidant can be estimated either by decrease in the intensity of dye colour, FG FCF for  $\text{KMnO}_4$ , GC for CAT due to disruption of chromophoric centers in the dye or by the development of colour with chromogenic reagent. The first step in the methods mentioned above is the oxidation of SRN with the oxidant.



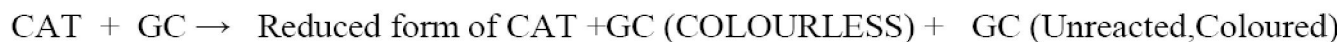
Exists as mixture of Compounds with rapture of conjugated system of FG FCF (Reproducible) but not Stiochiometric as several alternative pathways are possible.

**(b) Method B**

In this method, CAT undergoes hydrolysis in aqueous acid medium to give sodium hypochlorite followed by Hypochlorous acid. This reacts with SRN to form the relevant oxidant products, probably a mixture which



The second step concerns with the estimation of the un-reacted oxidant or the reduced form of oxidant



Exists as mixture of compounds with rupture of conjugated system in GC (Reproducible) but not stoichiometric as several alternative pathways are possible

**CONCLUSION**

The proposed methods are superior in one way or other (simplicity,  $\lambda_{\text{max}}$ , stability of coloured species) over very few visible spectrophotometric methods reported so far. It can be seen from the results presented above, that the proposed methods have good sensitivity. Stastical analysis of the results (TABLE 1) shows that the proposed procedures have good precision and accuracy. Results of the analysis of pharmaceutical formulations (TABLE 2) reveal that the proposed methods are suitable for their analysis with virtually no interference of the usual additives. All the proposed methods are simple, sensitive, and reliable and can be used for routine determination of SRN in bulk samples and pharmaceutical formulations depending upon the needs of the specific situation. Recovery experiments indicated the absence of interference from the commonly encountered pharmaceutical excipients present in pharmaceutical formulations.

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appears to be reproducible under the specified experimental conditions. The remaining Hypochlorous acid may be responsible for the bleaching of the colour GC through destruction of the extended chromophoric system.

with appropriate dye or chromogenic agent.

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