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Selective Membrane Sensors for the Determination of Sildenafil, Tadalafil and Vardanafil

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Selective sensors were developed for the estimation of Sildenafil, Tadalafil and Vardenafil. The membrane preparations are described by incorporating an appropriate ion exchangers with tetraphenyl borate or dinonyl naphthalene sulfonate and solvent mediator into a poly vinyl chloride matrixes. The potentiometric response was linear over the drug range of concentration between 1.0×10^{-6} to 1.0×10^{-2} mol/L and show a near-Nernstian with slope (53.70 ± 0.30a , 53.22± 0.54 or 54.42± 0.38, 53.61± 0.36 and 51.43± 0.25, 53.51± 0.53 mV/decade) for the three drugs , respectively depending on their nature. The selectivity of sensors was reported to different related compounds. The sensors were applied successfully for the estimation of these drugs in their formulations.

Keywords: Phosphodiesterase Type 5 Inhibitor drugs ; Selective membrane sensors; Potentiometric estimation; pharmaceutical formulations

1. INTRODUCTION

Potentiometry with selective sensors is very important techniques for the estimation of organic compounds in biological practice. Suitable drug sensors have enough selectivity towards the excipients, they are very useful in their estimation without prior separation. Potentiometric sensors posses many advantages over other methods and give fast, accurate, reproducible, regular and sensitive estimation.

Recently, Sildenafil; Sd, Tadalafil; Td and Vardenafil; Vd were known as selective inhibitors of Phosphodiesterase Type5; PDE5 [1-2]. The activity of Sd for the erectile dysfunction treatment has been published [3-8], its over dose might cause many side-effects[9-10].

Td is suitable for the treatment of mild to severe erectile dysfunction ; ED. Vd is absorbed rapidly within 15 minutes [11-12]. Men taking Vd show improvement after 12 weeks [13]. Medical

results have shown that Vd represents a valuable new therapy and most of patients were treated after using it [14].

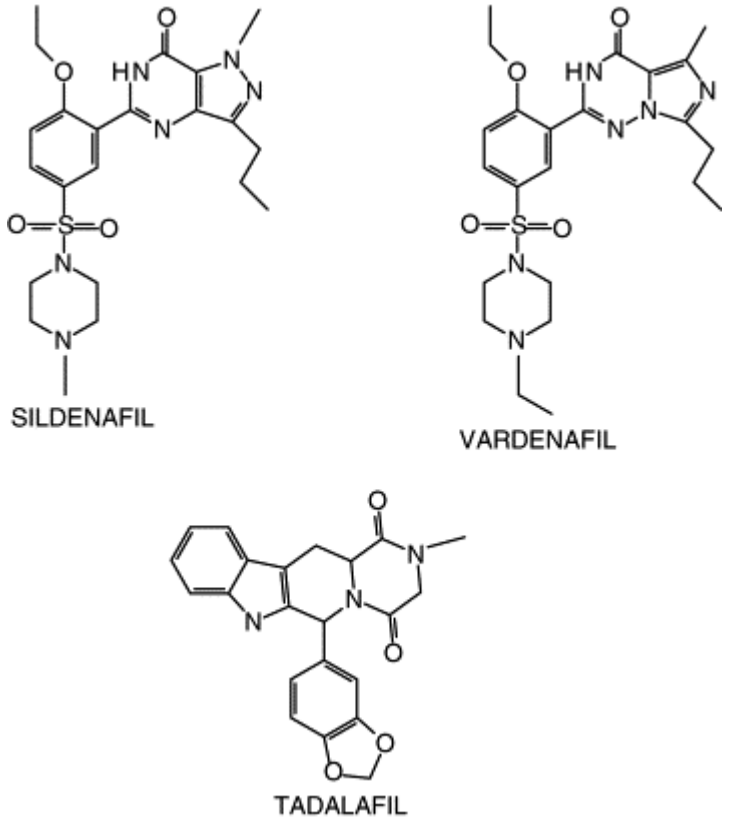

Figure 1. Chemical structures of Sd, Vd and Td.

No official method was reported for Sd estimation in dosage forms. Several spectrochemical, chromatographic and electro analytical methods[15- 37] have been listed for the estimation of Sd. These methods are very expensive, need certain treatments, non selective and taking time [16,19, 20, 26 and 28].

Vd has no official method for its estimation. Recently, new publications were listed for the determination of the three drugs [38-52]. However, all these techniques require sophisticated and expensive equipments which is not affordable for smaller laboratories, using rapid, simple, cheap and very sensitive procedure is desirable.

Since the quantitative detection of Sildenafil; Sd , Tadalafil ; Td and Vardenafil; Vd is important, sensors as simple, rapid, and low-cost devices can be used to monitor them. However, in recent years, the number of reports on developing these drugs -selective sensors are limited. Thus, it is challenging and still interest to design drug-selective sensors.

The present work describes the construction and evaluation of newly Phosphodiesterase Type5; PDE5 drug sensors. The active constituents in a polyvinyl chloride ; (PVC) matrix selective sensors are the cited drugs with tetra phenyl borate; TPB or naphthalene sulfonate; DNNS ion associate

complexes. The sensors are successfully applied for the estimation of the cited PDE5 drugs in the pure solutions and in some pharmaceutical formulations.

2. EXPERIMENTAL

2.1. Reagents and Materials

Sildenafil citrate; Sd (Asia Company for Pharmaceuticals, Sorya), Caverta, 100 mg Sd / tablet, Vega, 50 mg / tablet and Edegra, 50 mg / tablet. Tadalafil; Td (Eli Lilly Company, USA). Cialis,® 20 mg of Td. Vardenafil; Vd (Bayer Company, Leverkusen, Germany), Levitra, 10 mg Vd. All formulations were purchased locally. Sodium tetra- phenylborate and PVC were purchased from Aldrich, plasticizer; 2-nitrophenyl octyl ether was Fluka product and dinonyl naphthalene sulfonic acid (Pfaltz and Bauer).

2.2. Instrumentation

An Orion digital pH/milli voltmeter Model 701A; Cambridge was used for all potentiometric measurements. A single junction Ag/AgCl reference electrode was included with a combination sensor for measuring pH.

2.3. Complexes of PDE5 Drug - TPB

The ion-associate complexes PDE5 drug–TPB were precipitated by mixing 0.01 molar 20 ml of Sd, Td, or Vd with 20 ml 0.01 molar sodium tetraphenyl borate; NaTPB solution. The forming solid complexes were filtered, washed clearly using distilled water and dried by air.

2.4. Selective Electrodes Construction

The selective electrodes were constructed according to Moody and Thomas method [53]. The polyvinyl chloride ; PVC, the complex, and plasticizer were fine powdered, then adding tetra hydro furan as a volatile solvent. A suitable diameter disk was cutting and glued to the flat end of polyvinyl chloride ; PVC tubing with Tetrahydrofuran; THF. The body of the sensor was filled with 0.001molar solution of the specific sensor in all cases. The sensors under investigation combined with PDE5 drug–dinonyl naphthalene sulfonate; DNNS complexes were formed according to reported method[54], in case of DNNS the percent of sensor constituents was 4.0 m/m and (64.0% m/m) of o-nitro phenyl octyl ether as a plasticizer . The sensor was adapted by immersing for 24 hs in 0.01 molar drug solution of the drug and stored for rest period in the same solution.

2.5. Characteristics of the Electrode

The performance characteristics of the constructed sensors were diagnosed by measuring emf values between 1×10^{-2} - 1×10^{-6} molar of the specific sensor. All measurements were carried out with stable readings for approximately 15 seconds.

2.6. Potentiometric Estimation of PDE5 Sensors

The selective sensors were immersed with reference electrode of the Orion double-junction in 50 ml aqueous drug solution of 0.1 M ionic strength and at the optimum pH. They were equilibrated with continuous stirring, measuring emf values then comparing with the formed calibration graph. Standard drug solution 0.01 molar 5.0 ml was then added using the standard additions method. The unknown concentration of the cited drugs was estimated by using the formed graphs.

Five tablets containing Sd, Td, or Vd as the active material were crushed, transferred to a 500-ml calibrated flask containing 0.1 molar ionic strength solution. The selective sensor with Orion reference were soaked in 0.1 molar ionic strength solution as stated above.

2.7. Potentiometric Measurements of Selective PDE5 Sensors

A 0.1 molar ionic strength solution of 30 ml was added to 10-ml (containing 1–10 mg) of the selective drug solution, titrating the resulting solution versus a 0.01 molar standard sodium tetra phenyl borate solution, using the cited drug sensor as the indicator electrode. At the equivalence point, the volume of titrant was obtained in the same way. For the analysis of tablet, 25- 50 ml aqueous tablet solutions from stock were transferred into a 100 ml beaker and following the same steps as stated above.

3. RESULTS AND DISCUSSION

3.1. Membrane Composition

PDE5 cited drug sensors and organic amines, are combined with DNNS and NaTPB, resulting stable complexes. The TPB complexes formed were separated then, immersed in a PVC matrix, and DNNS complexes were formed in situ, by immersing the DNNS–PVC sensors in the selective sensor solution. 2-NPOE as a plasticizers showed good results. The sensor constituents were 4.0% m/m DNNS, 64.0% m/m 2-NPOE, and 32.0% m/m PVC; and 3.2% m/m drug–TPB, 64.5% m/m 2-NPOE, and 32.3% m/m PVC , respectively.

3.2. Sensors Characteristics

Table 1 show the resulting response characteristics for the cited sensors. The obtained data show

a near- Nernstian response for the three sensors with respect to DNNS - and TPB - sensors over a wide concentration range. The linear range was found to be depended on the nature of the drug.

Table 1. Electrochemical response characteristics of the proposed PDE5 Drugs Membrane Sensors

Parameter	Tadalafil		Vardenafil		Sildenafil	
	TPB-sensor	DNNS-sensor	TPB- sensor	DNNS-sensor	TPB- sensor	DNNS-sensor
Slope (mV/ log a)	53.70 ± 0.30[a]	53.22± 0.54	54.42± 0.38	53.61± 0.36	51.43± 0.25	53.51± 0.53
Intercept (mV)[b]	228± 2.4	224± 1.4	228± 2.1	224± 1.8	220± 2.5	227± 2.3
Linear range (M)[c]	$10^{-2} – 10^{-5}$	$10^{-2} – 10^{-5}$	$10^{-2} – 10^{-5}$	$10^{-2} – 10^{-5}$	$3\times10^{-3} – 10^{-5}$	$3\times10^{-3} – 3\times10^{-6}$
Detection limit (M)	1.0×10^{-5}	1.2×10^{-5}	1.4×10^{-5}	1.6×10^{-5}	1.7×10^{-5}	4.5×10^{-6}

[a] Stand. dev. av. slope value for several calibrations.

[b] Stand. dev. recorded in one month.

[c] Response range in sub-Nernstian region.

The linear range resulting in case of Sd was clearly shorter than that of Td and Vd. The limits of detection are similar for all sensors, except that for DNNS-built sensors, for Sd a detection limit of 4.5×10^{-6} M is obtained. This is due to DNNS forms a partially soluble complex with respect to Sd than other drugs. The forming calibration graphs were perfectly reproducible for all cases for all days, confirming the storage of sensors in their selective cited drug solution at rest period.

Generally, The three cited sensors accepted a near-Nernstian response within the range $10^{-2} – 10^{-4}$ M and in the range $10^{-4} – 10^{-6}$ M with respect to the TPB anions over-Nernstian response. The same results have been listed for a quinidine selective membrane [55] and also for membrane sensors formed by a PVC coating film [56].

3.3. Effect of pH

The pH effect on the potential reading of the cited sensors was compared by comparing the emf of a cell of the type Ag ‖ Ag Cl ‖ 10^{-3} M cited drug 0.1 M ionic strength (inner solution)\sensor \ 10^{-3} M cited drug 0.1 M ionic strength with that of the reference electrode with 10% m/v Na_2SO_4 in the outer part, adding (0.1 or 1.0 M HCl and/or NaOH solution each) to change acidity. The linearity of the potential (E) against pH depends on the drug nature (Fig.2). For Td and Vd, the response of the sensors is not influenced by low pH till pH 6.8 and 7.6, respectively.

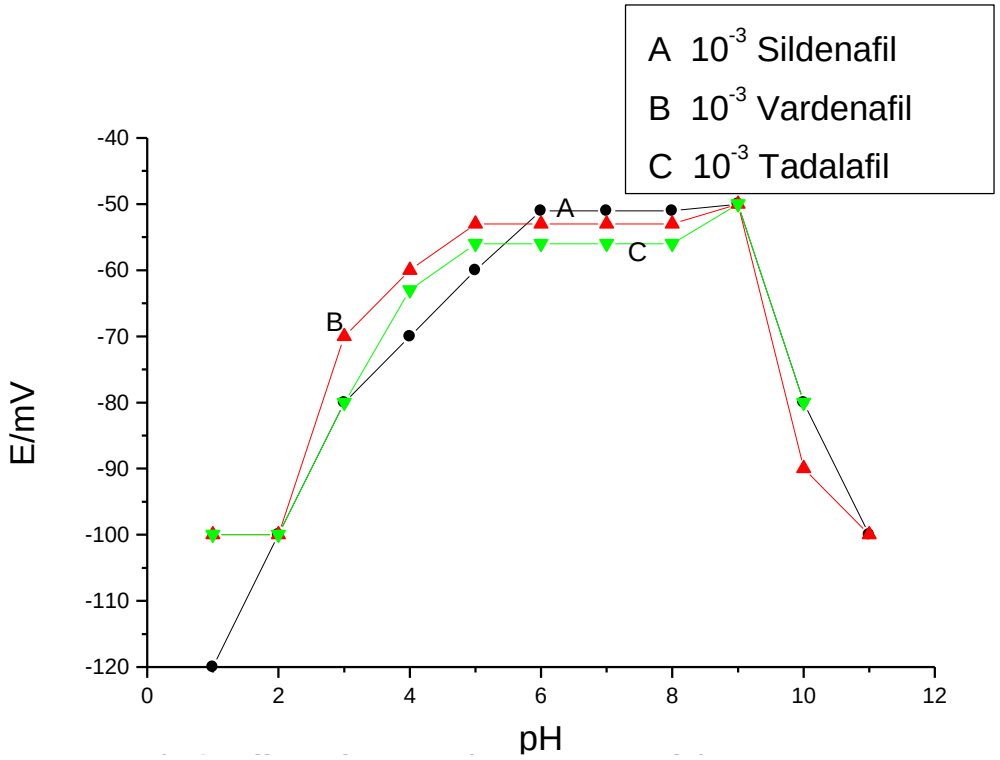

Figure 2. Effect of pH on the response of the PDE5-TBP-based membrane electrodes. The graphs are displaced vertically for clarity; similar graph shapes were recorded for DNNS-based membrane electrodes.

With respect to Sd, a linear potential was observed in the pH range from 4.5 to 6.5. By lowering pH, the Sd sensors become more sensitive to its species and the emf reading was decreasing directly with lowering pH. By increasing pH values of the test aqueous solutions, the Sd, Td and Vd free bases were precipitated and the concentration of the un-protonated species are increased gradually. Thus, the recorded emf readings will be decreased.

Fig. 2 was used to calculate the cited drug basicity constants (K_b). It was found that the pH value when the initial concentration of protonated PDE5 cited drug, pK_a ; acidity constant is halved, i.e., decreasing the potential by 0.28*S* mV (*S* = electrode slope). In case of Sd, (K'_b) the second basicity constant was estimated from (pK'_a) where the mono-protonated Sd, [SdH^+] initial concentration is also halved, i.e., when the Sd potential sensor decreases by the same value (0.28*S*). Table 2 show the resulting pK_b values of the PDE5 sensors under investigation.

Table 2. Basicity constants of the cited drugs estimated from potential versus pH Graphs[a]

PDE5 Drug	K_b	K_b'
Tadalafil	1.72×10^{-7}	----------
Vardenafil	1.22×10^{-6}	----------
Sildenafil	8.53×10^{-8}	2.65×10^{-11}

[a] The average of three values resulting from the two membrane sensors

3.4. Effect of foreign compounds

The sensor response toward other different compounds has been studied and $K^{pot}_{drug^+, J^{+z}}$, the selectivity coefficients were used to estimate the degree of interference. By using the separate solution method and eq. (1) we get the data listed at Table 3:

$$\log k^{pot}_{drug^+, J^{+z}} = (E_2 - E_1)/s + \log[drug^+] - \log[J^{+z}]^{1/z}, \quad (1)$$

Where E_1 is the PDE5 sensor potential of 0.001 M solution and I = 0.1 M ionic strength and E_2 is the same sensor potential in a solution containing [$drug^+$] = 0 and [J^{z+}] = 0.001 M at the optimum values of ionic strength and pH; J represents the interferent. The compounds reported at Table 3 were stated as low-level potential contaminants in the cited drug tablet samples.

The excipients of the tablets usually do not interfere. The same effect was also shown by other sugars, cellulose, croscarmellose sodium and triacetin. Table 3 show that in all cases the sensors have a very little interfering in their samples in presence of other compounds. From the PDE5 drug structures we can expected that , order of selectivity is Td- Vd - Sd. The greater selectivity of Td sensor over Vd because of Td is larger than Vd by 60 atomic mass units. This correlation between mass and hydrophobicity is not valid for Sd because it has a similar structure as Vd. This confirm the primarily determination of selectivity between aqueous and organic media [54].

Table 3. Selectivity Coefficients for the PDE5 Drug Sensors

Interferent , J	Selectivity Coefficient ($\log k^{pot}_{drug^+, J^{+z}}$)					
	Tadalafil		Vardenafil		Sildenafil	
	TPB-sensor	DNNS-sensor	TPB- sensor	DNNS-sensor	TPB- sensor	DNNS-sensor
Tadalafil	1.0	1.0	0.52	0.48	0.88	0.68
Vardenafil	- 0.65	- 0.55	1.0	1.0	0.17	0.07
Sildenafil	- 0.75	- 0.63	- 0.21	- 0.14	1.0	1.0
Dopamine	- 2.06	- 2.64	- 1.82	- 1.95	- 1.93	- 2.43
Acetylcholine	- 2.12	- 2.61	- 1.86	- 2.33	- 2.01	- 2.56
Glycine	- 1.67	- 2.32	- 1.86	- 2.11	- 1.78	- 2.35
Quinidine	- 1.67	- 1.42	- 1.43	- 1.33	- 1.20	- 1.33
Quinine	- 1.87	- 1.75	- 1.56	- 1.48	- 1.42	- 1.45
$(CH_3)_4N^+$	- 2.18	- 2.70	- 2.03	- 2.45	- 2.08	- 2.21

In general, Table 3 show that the PDE5 sensor based-DNNS sensor have a greater selectivity than PDE5 sensors based – TPB.

3.5. Response Time

The dynamic response time of the cited Td and Vd sensors in both kinds and also in case of Sd based– TPB sensor was fast, in the range 10^{-2} – 10^{-4} M needing less than 1 min with 10^{-5} M solution. While, in case of Sd based– DNNS sensor, a 4-5 min response time was recorded over the range 10^{-5} – 10^{-6} M. Also, in this range the emf values were found to be reproducible.

3.6. Analytical Applications

All PDE5 drug sensors confirmed a useful potentiometric estimation of the cited PDE5 drugs in pure solutions or in tablets,(Tables 4 and 5) using potentiometric titrations and direct potentiometry. Greater emf breaks were resulted with DNNS-built sensors, but calibration graphs were shifted after one potentiometric titration by several millivolts. By immersing the sensors in 0.001 molar solution of the suitable PDE5 drug for about 2h the starting response was restored. From these results, we recommended TPB-based sensors for use in potentiometric titration where the calibration graph is maintained in these examples.

Table 4. Analysis of PDE5 Drugs in Pure form with the Proposed Sensors.

PDE5 drug	Taken amount (mg) (range)	Recovery[a] (%)		Standard deviation[c] (%)	
		Potentiometric titration[b]	Standard additions method	Potentiometric Titration	Standard additions method
Tadalafil	1.74 – 8.82	99.20	100.50	0.86	1.70
Vardenafil	1.58 – 8.09	100.20	101.52	0.45	1.93
Sildenafil	0.86 – 4.62	101.20	99.40	0.86	2.16

[a] Taken amount; the averages of 5 estimations.

[b] In all instances, TPB-sensors were used; the sildenafil-DNNS-sensor was used only in the stand. additions method for Sd estimation.

[c] Total Volume = 50 ml (I = 0.1 M, adjusted with NaCl), V(sample) = 2 or 5 ml, and sample concentration= 10^{-2} M solution of respective PDE5 sensor

Table 5. Analysis of PDE5 Drugs in Dosage Forms using PDE5 Sensors[a].

Product (Active principal)	Result (% of nominal)		Standard deviation[c] (%)	
	Potentiometric titration[b]	Standard additions method	Potentiometric Titration	Standard additions method
Cialis (20 mg Td HCl / tablet)	99.8	100.6	0.82	2.52
Levitra (10 mg Vd HCl/ tablet)	100.4	100.1	0.53	1.48
Edegra (50 mg Sd cit./ tablet)	98.7	99.3	0.65	1.32
Caverta (100 mg Sd cit./ tablet)	98.9	99.5	0.76	1.28
Vega (50 mg Sd cit./ tablet)	98.6	99.2	0.68	1.04

[a] In all cases, TPB-sensors were used [b] The averages of 5 estimations.

[c] The averages of 7 – 10 estimations.

The results of potentiometric estimation examined in pure solutions of the cited sensors, using standard additions and potentiometric titrations with 0.001 molar aqueous NTPB are shown at Table 4, the potentiometric analyses of the cited PDE5 tablets are listed at Table 5.

3.7. Comparison with the literature

The results obtained by the developed electrodes method were statistically analyzed and compared with those obtained by other different reported methods. Table 6 presents comparative characteristics of the quantitative estimation of Sd, Td and Vd drugs in pharmaceutical formulations using different methods cited in the literature. The calibration curves provided reliable linear responses on a suitable range. Most of the methods show a good recovery with respect to the labeled values and there is no interference from the common excipients present in the tablet formulations. No significant differences for either accuracy or precision were observed.

Table 6. Comparison of Analytical Parameters of Different Methods for Sd, Td and Vd Estimation

Method	Slope (mV)	Linear Range (M)	Detection Limit (M)	Ref.
Present Method Sd - TPB	51.43± 0.25	$3x\ 10^{-3}$ - $3 x\ 10^{-5}$	$1.7 x\ 10^{-5}$	----
Present Method Sd - DNNS	53.51± 0.53	$3x\ 10^{-3}$ - $3 x\ 10^{-6}$	$4.5 x\ 10^{-6}$	
UV-Sd -Chromoxane cyanine	------	$1.5x\ 10^{-3}$ - $6 x\ 10^{-3}$	$1.8 x\ 10^{-4}$	33
Sd- Spectrophoto.	------	$4 x\ 10^{-4}$ - $2.5 x\ 10^{-4}$	$1.2 x\ 10^{-6}$	34
	------	$5 x\ 10^{-4}$ - $9 x\ 10^{-4}$	$1.6 x\ 10^{-6}$	
Sd- RP-HPLC	------	$5 x\ 10^{-4}$ - $8 x\ 10^{-5}$	-------	
Sd- Micellar Electrokin Capil	------	$1 x\ 10^{-3}$ - $2 x\ 10^{-4}$	$1.9 x\ 10^{-4}$	35
Sd- Ion-Sel. Electrode	57.20	$3.4x\ 10^{-5}$ - $1.7 x\ 10^{-3}$	$3 x\ 10^{-7}$	37
Sd- Ion-Sel. Electrode - PMA	55.50± 0.35	$5 x\ 10^{-5}$	$5 x\ 10^{-6}$	31
Sd- Ion-Sel. Electrode - TPB	53.50± 0.50	$5 x\ 10^{-5}$	$6 x\ 10^{-6}$	
Sd-Brilliant blue Spectroph.	------	$1 x\ 10^{-5}$ - $4 x\ 10^{-4}$	$4.83 x\ 10^{-6}$	36
Sd-Bromocresol Purple Spectroph.	------	$2.1 x\ 10^{-5}$- $1.5 x\ 10^{-4}$	$7.24 x\ 10^{-6}$	
Present Method Td - TPB	53.70± 0.30	10^{-2} - 10^{-5}	$1.0 x\ 10^{-5}$	-----
Present Method Td - DNNS	53.22± 0.54	10^{-2} - 10^{-5}	$1.2 x\ 10^{-5}$	
Td- Spectroph.	------	$1.8 x\ 10^{-3}$- $6 x\ 10^{-4}$	$1.05 x\ 10^{-4}$	38
Td- Spectroph.	------	$1.0 x\ 10^{-4}$- $5.5 x\ 10^{-4}$	$2.3 x\ 10^{-4}$	39
Td- Spectroph.	------	$2.0 x\ 10^{-3}$- $2.0 x\ 10^{-4}$	$1.1 x\ 10^{-4}$	40
Td- Spectroph.	------	$1.0 x\ 10^{-3}$- $1.5 x\ 10^{-4}$	$2.7 x\ 10^{-4}$	41
Present Method Vd - TPB	53.70± 0.30	10^{-2} - 10^{-5}	$1.2 x\ 10^{-5}$	-----
Present Method Vd - DNNS	53.70± 0.30	10^{-2} - 10^{-5}	$1.2 x\ 10^{-5}$	
Vd- Spectroph.	------	$1.0 x\ 10^{-3}$- $0.8 x\ 10^{-4}$	$2.4 x\ 10^{-4}$	41
	------	$1.0 x\ 10^{-3}$- $1.2 x\ 10^{-4}$	$2.8 x\ 10^{-4}$	
Vd- Spectroph.	------	$0.4 x\ 10^{-4}$- $6.0 x\ 10^{-4}$	$3.5 x\ 10^{-6}$	43

Vd- Spectroph.	------	1.0×10^{-3}- 1.2×10^{-4}	2.7×10^{-4}	44
Vd- Spectroph.	------	4.0×10^{-3}- 4.0×10^{-4}	4.4×10^{-5}	45
Vd- Spectroph	------	4.0×10^{-3}- 6.0×10^{-4}	3.5×10^{-5}	

By potentiometric titrations good precise and accurate results were resulted. The standard additions method is simple and fast so, we also recommended the results produced from it. The consuming time (two hrs.) required for estimation by the official method[57] while the sensor assay by the present work can be proved within 15 min. This rapidity with those sensors makes them practically suitable for estimation a single and tablet- to-tablet variation if wanted.

4. CONCLUSIONS

As a result of the experiments conducted in this study, we conclude that new sensor membranes were developed for the estimation of the three cited drugs Sildenafil, Tadalafil and Vardenafil in pure solution and pharmaceutical formulations.

Generally, The three cited sensors accepted a near-Nernstian response within the range 10^{-2} – 10^{-4} M and in the range 10^{-4} – 10^{-6} M with respect to the TPB anions over-Nernstian response. The same results have been listed for a quinidine selective membrane [55] and also for membrane sensors formed by a PVC coating film [56]. The developed sensors method was found as precise and accurate as compared to other reported techniques which is widely used in their estimation in pharmaceutical formulation Table 6.

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