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A NOVEL RAPIDLY DISINTEGRATING TABLET OF SILDENAFIL CITRATE WITH ENHANCED STABILITY: DESIGN AND *IN-VITRO* EVALUATION

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ABSTRACT

This work aimed to formulate sildenafil citrate rapidly disintegrating tablets with enhanced stability utilizing the approach of incorporating antioxidant simultaneously with pH modifier for adjusting the tablet microenvironmental pH. Studies for effect of pH on the drug saturated solutions stability revealed that the drug exhibited maximum stability at pH 4.6. Studies for the effect of antioxidants on drug stability revealed marked stabilizing effect of sodium metabisulphite. Tablets were prepared by direct compression according to 2^2 factorial design considering the factors; filler and disintegrant types. All blends contained sodium metabisulphite as antioxidant and potassium dihydrogen phosphate as microenvironmental pH adjuster. Two-way ANOVA was performed to assess effects and interactions of formulation factors on tablets characteristics. Two selected formulae (F b and F ab) were subjected to storage at 50 ºC/75 % R.H for 12 weeks, where no significant changes was observed for F ab, while marked discoloration was observed for F b. The results suggested that F ab could be a promising drug formulation with rapid disintegration and enhanced stability.

Keywords: Sildenafil citrate, rapidly disintegrating, microenvironmental pH, Factorial design

INTRODUCTION

Sildenafil citrate is a selective phosphodiesterase-5 inhibitor indicated in the treatment of erectile dysfunction (1). It was primarily meant for the treatment of angina and hypertension but found to have a strong positive effect on sexual performance. Subsequently it was successfully investigated for the oral treatment of erectile dysfunction and was approved by the FDA in March 1998 (2). Many patients may prefer the oral route of administration to the more invasive other treatment options, especially if the oral formula could achieve a rapid onset of action. However, it is reported that the medicine should be stored below 40°C preferably between 15°C and 30°C (3), away from direct light and damp places (4). The degradation of the drug is reported to be oxidative-induced (5). Oxidation processes may proceed slowly under the influence of atmospheric oxygen (auto-oxidation), or may involve the reversible loss of electrons without the addition of oxygen. The oxidative process is usually diverted and the stability of the drug is preserved by antioxidants (6).

In many cases, it is more difficult to remove electrons from a drug which is more positively charged. For this reason, drug stability against oxidation is often greater under lower pH conditions which promote the protonation of drugs if protonation is possible. In converse, higher pH conditions which deprotonate a drug, generally make that drug more susceptible to oxidation (6). pH is not a defined term in solid systems, however, in all solid dosage formulations there will be some free moisture (contributed by excipients as well as the drug), and certainly in tablets a significant percentage, typically 2% w/w, that is required to facilitate direct compression (7). The dissolution of both the drug and the excipients in this free water confers a certain pH to the

microenvironment of the tablets (8). Therefore, if the compound is more stable in an acid than in a neutral or basic environment, it may be formulated with solid acids; conversely, if it is acid-sensitive, bases should be employed in an attempt to make an adjustment of the microenvironmental pH, i.e. buffering a solid dosage form (7).

The approach of microenvironmental pH adjustment has been used by Badawy *et al.* (9) to improve the stability of an ester prodrug of a fibrinogen glycoprotein IIb/IIIa receptor antagonist. A screening model to identify the effect of microenvironmental pH of the drug-excipient mixture on solid dosage forms was described by Serajuddin et al (10).

A method for the determination of sildenafil citrate in the presence of its oxidative-induced degradation products using reversed phase HPLC was described by Segall *et al.* (5). However, literature lacks any data about the use of antioxidants and microenvironmental pH adjustment as an approach to enhance the stability of the drug as well as, its formulation in the form of rapidly disintegrating tablets. Thus, the aim of this work was to investigate the effect of different pH values and different antioxidants on the stability of sildenafil citrate, and to select the most appropriate microenvironmental pH adjuster and antioxidant to be incorporated in the prepared tablets. The drug was then formulated in the form of rapidly disintegrating tablets and the prepared tablets were evaluated for weight variation, content uniformity, friability, hardness, disintegration and *in-vitro* dissolution. In addition, the effect of storage at 50 ºC/75 % R.H for twelve weeks on the properties of the selected tablet formulations was investigated.

MATERIALS AND METHODS

Materials: Sildenafil citrate (Memphis company, Egypt). Sodium metabisulphite was obtained from Prolabo (France). Avicel PH 102 and Ac-Di-Sol were obtained from FMC corp. (Pennsylvania, USA). Spray-dried lactose was obtained from Meggle (Germany). Explotab® was obtained from JRS Pharma (Germany). All other chemicals and solvents were of analytical grade and used without further purification.

Effect of pH on the stability of sildenafil citrate: The effect of different pH values namely; 3.4, 4, 4.6, 5.2 and 5.6 on the stability of saturated solutions of sildenafil citrate was studied using McIlvaine citrate buffer. The prepared solutions were stored in transparent glass vials at a temperature of 60°C for a period of 35 days (10). Samples were taken after 7, 14, 21 and 35 days and analyzed for the percent remaining sildenafil citrate spectrophotometrically at 257.4 nm (UV-1601 PC, Shimadzu, Japan) using a stability-indicating ratio derivative spectrophotometric assay developed and validated in our laboratory (unpublished data). Statistical analysis of the results was performed using two way ANOVA test the significance of the pH values on the percent drug remaining at different time intervals at $p \leq 0.05$. Subsequent Fisher's PLSD test was then performed to determine the source of difference.

Effect of different antioxidants on the stability of sildenafil citrate: The effect of antioxidants namely; thiourea, ascorbic acid and sodium metabisulphite on the stability of saturated solution of sildenafil citrate was studied. Saturated solutions of sildenafil citrate in McIlvaine buffer was prepared at the pH corresponding to that of maximum stability (pH 4.6). The aforementioned antioxidants were added to the prepared solutions at a concentration of 0.1%. The solutions were stored in transparent glass vials at a temperature of 60°C for a period of 35 days (10). The percent sildenafil citrate remaining at different time intervals was assayed spectrophotometrically at 257.4 nm (UV-1601 PC, Shimadzu, Japan) using a stability-indicating ratio derivative spectrophotometric assay developed and validated in our laboratory (unpublished data).

Formulation of sildenafil citrate rapidly disintegrating tablets: A full 2^2 factorial design was used. The factors considered were the filler type (Avicel PH 102 and spray-dried lactose) and the disintegrant type (Ac-Di-Sol and Explotab). Preliminary formulation studies were performed to ensure the absence of incompatibilities between the drug and the selected excipients (data not shown). The factors used in the 2^2 factorial design and their levels are shown in table (1). Four tablet formulae were prepared containing drug, filler, disintegrant, lubricant (magnesium stearate) and antioxidant (sodium metabisulpite) . In all formulae, the drug concentration was held constant at 70 mg sildenafil citrate (equivalent to 50 mg sildenafil base) per 400 mg formulation (tablet weight). The disintegrant, lubricant and antioxidant concentrations were also kept constant at 2%, 1% and 0.1% of the tablet weight respectively. These concentrations were chosen as guided by the preformulation study.

Adjustment of the microenvironmental pH of the prepared blends: The approach of incorporating a pH modifier (9) in the formulations was used to control the microenvironmental pH to coincide with that

corresponding to the maximum stability of sildenafil citrate. Saturated solutions of different acidic components, namely; citric acid, fumaric acid, monosodium citrate and monobasic potassium phosphate (potassium dihydrogen phosphate) were prepared and the pH of each solution was determined using a pH meter (Schott-Geräte, GmbH, Germany). The effect of the previously mentioned acidic substances on the microenvironmental pH of the prepared blends was tested in concentration of 1% (9). The microenvironmental pH of each blend was estimated by preparing saturated solution of the blend in distilled water, and then recording its pH. It was necessary that the solid remained in equilibrium with the liquid phase since variation in pH was observed if filtered solutions were used (10).

Characterization of the powder blends to be compressed: The blends were prepared by geometric dilution followed by 10 minutes mixing in cubic mixer (Erweka-Type KU1, Erweka apparatebau, Heusenstamm, Germany) after adding the lubricant. Analysis of random samples of the blends indicated adequate uniformity of mixing. Table (2) shows the composition of the prepared tadalafil tablet formulae according to the experimental design used.

Bulk density and compressibility measurements: A known quantity of each blend (5 grams) was poured through a funnel into a 25-ml graduated cylinder. The cylinder was then lightly tapped twice to collect all the powder sticking on the wall of the cylinder. The volume occupied was then read directly from the cylinder (initial bulk volume; V_b) and used to calculate the initial bulk density (ρ_b) according to the mass/volume ratio. For the tapped bulk density (ρ_t), the cylinder was tapped at a constant velocity on a wooden bench top, until a constant volume was attained (tapped volume; V_t) (12). % compressibility (Carr's index) was then determined from the equation: Carr's index = $[(\rho_t - \rho_b)/\rho_t] \times 100$ (13). Hausner ratio was obtained by dividing ρ_t by ρ_b (14).

Determination of flowability: The fixed height cone method was adopted (15). A cut-stem glass funnel was tightened at a height of 2.5 cm from a horizontal plane. The powder sample was allowed to flow gently through the funnel till a cone was formed and touched the funnel surface orifice. Powder flow was then stopped and the average diameter of the formed cone (d) was determined. The angle of repose (θ) was calculated from the equation: $\tan \theta = 2h/d$ where, h is the height of the cone formed by the powder (mm) and d is the diameter of the cone (mm).

Preparation of sildenafil citrate rapidly disintegrating tablets: Sildenafil citrate rapidly disintegrating tablets were prepared using the compressible blends prepared previously. The blends were compressed with a single punch machine into 400-mg tablets using 0.4 inch punch and die. The force of compression was kept constant such that tablets varied in hardness from formulation to another as a reflection of the effect of the directly-compressible vehicles (fillers) used.

In-vitro characterization of the prepared tablets: The tablets were evaluated for weight variation and content uniformity according to the method adopted by the B.P. (16). Friability test was carried out using a tablet friabilator (Model DFI-1, Veego, India) according to the B.P. (16). Hardness of the prepared tablets was determined using hardness tester (Monsanto, USA) (17). Disintegration was performed using USP disintegration tester (Model DST-3, Logan Instruments corp., USA) and following its procedures (18).

In-vitro dissolution of the prepared tablets: The dissolution of sildenafil citrate from its tablets was performed according to the rotating basket method using a USP dissolution tester, apparatus II (VK 700, Vankel, USA) in 900 mL of 0.1 N HCl. The stirring speed was 50 rpm and the temperature was maintained at 37 ± 0.5 ºC. Aliquots each of 5 ml from the dissolution medium were withdrawn at 2, 4, 6, 8, 10, 15, 30 and 45 minutes time intervals. The samples withdrawn were then filtered, adequately diluted and analyzed spectrophotometrically for sildenafil citrate content by measuring the absorbance at λmax (UV-1601 PC, Shimadzu, Japan). A similar volume of 0.1 N HCl was added to the dissolution medium in order to maintain the volume in the vessel constant. Each experiment was carried out in triplicate.

Statistical analysis: Two-way analysis of variance (ANOVA) test was performed to assess the significance of the different formulation factors and the interactions between these factors on tablets' hardness, disintegration and percent drug dissolved after 10 minutes using the StatView® software, version 4.75 (Abacus Concepts Inc., Berkeley).

Effect of storage on the physical properties and in-vitro dissolution of selected tablet formulae:

The selected sildenafil citrate tablets formulae were stored at a temperature of 40 , 50 and 60 ºC/ 75% R.H. (maintained using a saturated solution of NaCl (19) for a period of three months. The stored tablets were examined visually for any changes in colour and/or appearance every week. Evaluation of the tablets' hardness, friability, disintegration and

dissolution was repeated at the end of the storage period for the tablets stored at 50 ºC/ 75% R.H.. The tests were performed using the same procedures adopted for the fresh tablets. The samples withdrawn during the dissolution studies were analyzed using the proposed stability-indicating method (instead of direct measurement of absorbance as in case of fresh tablets).

RESULTS AND DISCUSSION

Effect of pH on the stability of sildenafil citrate: Fig. 1. illustrates the effect of the various acidic pH values, namely; 3.4, 4, 4.6, 5.2 and 5.6 on the stability of sildenafil citrate saturated solutions in McIlvaine buffer after storage at 60°C for 35 days. It is clear that the maximum stability of the drug corresponding to the highest percent drug remaining (81.82 %) at the end of the storage period existed at pH 4.6. The results obtained were compared to those obtained from direct spectrophotometry at λ_{max} 292 nm where the percent drug remaining was found to be 99-101%. The difference between the results obtained from both methods could be attributed to the presence of the degradation product of sildenafil citrate which interferes with the determination of the drug at its λ_{max} using direct spectrophotometry, while the developed first derivative ratio spectra method could successfully solve this problem. The degradation product was further confirmed by TLC on silica gel plates, using ether : dichloromethane : methanol (5 : 19.5 : 5, v/v/v) as a mobile phase. Statistical analysis of the obtained results using two-way ANOVA showed a significant difference between different pH values and different time intervals at $p \leq 0.05$. Subsequent multiple comparisons Fisher's PLSD showed that pH 4.6 differs significantly from pH 3.4, 5.2 and 5.6, while there is no significant difference between pH 4.6 and pH 4 at $p \leq 0.05$. Therefore, sildenafil citrate saturated solutions were proved to be more stable within the pH range 4 to 4.6 compared to other pH values.

Effect of different antioxidants on the stability of sildenafil citrate: The effect of the antioxidants namely; ascorbic acid, thiourea and sodium metabisulphite on the stability of sildenafil citrate saturated solutions in McIlvaine buffer (pH 4.6) was studied after storage at 60°C for 35 days. The stored solutions were inspected daily for any change in colour or appearance and subjected to chemical stability testing at the specified time intervals using the developed first derivative of the ratio spectra method of assay. The solutions containing ascorbic acid as antioxidant developed a dark yellow colour after storage for two days, this may be attributed to the instability of ascorbic acid in aqueous solutions (20), especially at higher temperatures. Therefore, the use of ascorbic acid was excluded. UV scanning of 0.1% thiourea in McIlvaine buffer revealed that it exhibits a prominent peak at λ 252 nm. This peak led to a strong interference with the peak amplitude at λ 257.4 nm in the first derivative of the ratio spectra used for the assay of drug, therefore the use of thiourea was excluded. Fig. 2. shows the effect of using 0.1% sodium metabisulphite as antioxidant on the stability of sildenafil citrate saturated solutions at pH 4.6 (McIlvaine buffer). It was evident that the mean percent sildenafil citrate remaining was higher in the presence of the antioxidant. The results obtained were compared to those obtained from direct spectrophotometry at λ_{max} 292 nm where the percent drug remaining was found to be 99-101%. The difference between the results obtained from both methods could be attributed to the presence of the degradation product of sildenafil citrate which interferes with the determination of the drug at its λ_{max} using direct spectrophotometry, while the developed first derivative ratio spectra method could successfully solve this problem. The degradation product was further confirmed by TLC on silica gel plates, using ether : dichloromethane : methanol (5 : 19.5 : 5, v/v/v) as a mobile phase. Two-sided unpaired t-test for the mean percent drug remaining in case of absence and presence of sodium metabisulphite revealed a significant difference between the mean percent remaining in each of the two cases at $p \leq 0.05$. Thus, sodium metabisulphite was found to have a marked stabilizing effect on sildenafil citrate. These results were in good agreement with the work of Ho and Wong (21) who found that the degradation rate of vitamin K1 was markedly reduced using sodium metabisulphite.

Adjustment of the micro environmental pH of the prepared blends: Table 3&4 show the saturated solution pH values of the acidic compounds; citric acid, fumaric acid, monosodium citrate and monobasic potassium phosphate (potassium dihydrogen phosphate) and the effect of these acids on the microenvironmental pH of the prepared blends, respectively. It was obvious that the pH values of the blends containing acidic compounds were lower than that of the blends devoid of any acid. Also, they were in good agreement with the corresponding saturated solution pH of the acid, i.e. the effect of an acid on the micro environmental pH of the blend could be predicted by the saturated solution pH of that acid. These results were in accordance with those found by Badawy *et al.* (9) who studied the effect of different acids on the

microenvironmental pH of an ester prodrug of a glycoprotein IIb/IIIa receptor antagonist blends. Among all the acidic compounds tested, potassium dihydrogen phosphate was found to adjust the micro environmental pH of the blends to that of maximum drug stability (pH 4-4.6). Therefore, potassium dihydrogen phosphate was selected to be incorporated as a pH modifier in sildenafil citrate formulation blends to adjust the micro environmental pH to that of maximum drug stability. This result is in agreement with the work of Krögel and Bodmeier (22) who used potassium dihydrogen phosphate as a buffering agent to adjust the pH within the enzyme-degradable plug of a capsular shaped pulsatile drug delivery system near the enzyme's optimum pH, thus improving the enzymatic activity.

Characterization of the powder blends to be compressed: Table 5. shows the physical properties of the powder blends of the tablet formulae compared to those of the pure drug. The blends of all formulae showed good to fair flow properties with respect to their Carr's index values which ranged from 17.89 % to 21.68 % (23). Also, Hausner ratio values of all the blends (except F ab, which exhibited a slightly higher hausner ratio of 1.277) were less than 1.25, indicating low interparticle friction and thus, good flow properties (23). In addition, the angles of repose of all the blends ranged from 34.14 ° to 35.03 ° indicating reasonable flow properties (24).

In-vitro characterization of the prepared tablets: Table 6. shows the characteristics of the prepared tablet formulations. None of the tablets deviated from the average weight by more than 5%, indicating that all formulae fulfill the pharmacopoeial specifications for weight variation (16). The average drug content of all formulae lies within the range of 85% to 115% of the label claim and the standard deviation is less than 6%, indicating that all formulae were complying with the pharmacopoeial limits regarding drug content (16). The percent friability of the prepared formulae was less than 1 % which conforms with the acceptable range for compressed tablets (16).

The prepared formulae showed hardness values ranging from 6.5 to 9 Kg. Statistical analysis of the hardness values, performed using two-way ANOVA, revealed that the filler type exhibited a significant effect on the hardness of the prepared tablets at $p \leq 0.05$. However, neither the disintegrant type nor the two-way interactions between the filler type and the disintegrant type showed any significant effect on hardness at $p \leq 0.05$. Needless to say that, using Avicel PH 102 as a filler significantly increased the hardness compared to spray-dried lactose at $p \leq 0.05$. However, the effect of Avicel did not depend on the type of disintegrant used. This is verified by the comparatively increased hardness of the formulae containing Avicel whether Explotab or Ac-Di-Sol is used as disintegrant (formulae a and ab). This might be attributed to the hydrogen bonds formed among the hydroxyl groups of the adjacent cellulose particles of Avicel, which are brought closely together by plastic deformation during compression (25, 26). The prepared tablets showed disintegration times ranging from 10 to 22 seconds. Statistical analysis of the disintegration times, performed using two-way ANOVA, revealed that both factors; filler type and disintegrant type, exhibited a significant effect on the disintegration time of the prepared tablets at $p \leq 0.05$. On the other hand, no significant interaction was found between both factors at $p \leq 0.05$. It was quite clear that using Avicel as a filler significantly decreased the disintegration time as evidenced by relatively faster disintegration of formulae a and ab compared to that of formulae (1) and b. Also, the use of Ac-Di-Sol as a disintegrant resulted in a significant reduction in the disintegration time as verified by the comparatively enhanced disintegration of formulae b and ab compared to formulae (1) and a. However, the effect of the filler type was higher and more statistically significant than the disintegrant type as verified by its higher F-value. The significant effect of the filler type might be due the difference in the mechanism of action of both Avicel and lactose. Avicel is an insoluble swellable material with good disintegrating properties, attributed to either capillary action or swelling (26). On the other hand, spray-dried lactose is not a swellable material and its action is due to slow dissolution rather than disintegration (27). Therefore, upon contacting the disintegration medium, the pores present in tablets containing lactose will be enlarged by the dissolution of lactose particles, so that the swelling of the disintegrant used (whether Ac-Di-Sol or Explotab) will have less effect on the destruction of the tablet matrix as compared to the tablets containing the more insoluble Avicel (26). Needless to say that, although increasing pore size causes rapid penetration by the disintegration fluid, yet, the disintegrant particles begin to swell and fill the void space without immediately affecting the tablet disintegration (28). It is worthy to note that, both Ac-Di-Sol and Explotab are "super-disintegrants" whose actions are mainly due to swelling. The previous results revealed that formula ab showed statistically lower disintegration time compared to the other formulae.

In-vitro dissolution of the prepared tablets: The dissolution profiles of the prepared tablets in 0.1 N HCl are demonstrated in Fig. 3. The reported values

are the arithmetic mean of three measurements ± standard deviations. The percentage drug dissolved was calculated according to the drug content determined for each formula. The dissolution profiles of all formulae were biphasic. The first phase was a rapid dissolution starting from zero to about 10 minutes, where more than 80% of the drug was released. This was followed by a second phase where the release was almost leveled during the rest of the study period. It was interesting to notice that, there was an initial flush dissolution which was more pronounced in the formulae containing lactose than in formulae containing Avicel.

This might be attributed to the fact that lactose is soluble in water and therefore, does not interfere with the water uptake needed for the drug dissolution. On the other hand, cellulose is insoluble in water and has great water uptake capacity, decreasing the initial availability of the medium to dissolve the drug (29). Another reason for the different behaviour could be the filler relationship to the drug particles inside the tablets. While lactose allows an immediate contact of the dissolution medium with the drug, Avicel permeates the dissolution medium into the compact mass, decreasing the initial drug contact with the dissolution medium (30). However, inspite of this difference in the initial flush dissolution, all formulae whether containing Avicel or lactose released more than 80% of the drug within 10 minutes. This might be because although Avicel is insoluble, yet it promotes rapid aqueous penetration into the tablet matrix through capillary action causing rapid disintegration by breaking hydrogen bonds between the bundles of cellulose microcrystals, thus promoting drug dissolution (31). Statistical analysis of the percent drug dissolved after 10 minutes (DP_{10}), performed using two-way ANOVA, revealed that neither the filler type nor the disintegrant type exhibited any significant effect on the dissolution of the prepared formulae. In addition, the filler-disintegrant interaction was also non significant on the drug dissolution.

The previous statistical analysis showed that Avicel (as a filler) and Ac-Di-Sol (as a disintegrant) showed better disintegration compared to spray-dried lactose and Explotab, respectively. However, both Avicel and spray-dried lactose did not differ significantly regarding their effect on the dissolution of the drug. Therefore, it was decided to study the stability of formulae containing Ac-Di-Sol (with faster disintegration property) whether lactose or Avicel were used as fillers (Formulae b and ab).

Effect of storage on the physical properties and in-vitro dissolution of the selected tablet formulae

None of the tablets stored at 40°C or 50°C/75% R.H. showed any changes in the colour or appearance throughout the storage period. However, regarding the prepared tablets stored at 60°C/75% R.H., only formula ab remained unchanged throughout the storage period. On the other hand, formula b showed very faint discolouration by the 10^{th} week. The discolouration then increased till developing a brown colour at the end of the storage period (12 weeks). This might be due to the presence of high percentage of lactose in such formula. Lactose is reported to undergo a non-enzymatic browning reaction with amines, generally known as Maillard reaction. Although this reaction is believed to occur mainly in primary amines (32), the possible interaction between the protonated pyrimidine nitrogen of sildenafil citrate and the free lactose carbonyl group should be considered (33). The characteristic and *in-vitro* dissolution parameters of the tablets stored at 50 ^{o}C/75 % R.H. for twelve weeks are listed in Table 7.

It was clear that hardness of both formulae decreased while the disintegration time increased. Both formulae showed slight decrease in the dissolution pattern (5.06 and 7.90 % decrease compared to the initial values, at the 10 minute dissolution time for formula b and ab respectively). The reduction in tablets' strength could be explained by the absorption of moisture by the disintegrant, thus causing swelling and bond disruption (34). It is worthy to note that formula b showed marked reduction in tablet hardness (more than 30%). This might be due to the dissolution of contact points between the individual lactose particles and decreased binding strength between them by virtue of moisture uptake (35, 36). The increase in the disintegration time of all formulae could be attributed to the moisture uptake by the disintegrant, which caused such disintegrants to lose some of their absorption and swelling abilities, thus extending the disintegration time (34). Based on the previous results F ab is suggested to be a promising tablet formulation of sildenafil citrate with rapid disintegration characteristics and enhanced physical and chemical stability.

CONCLUSION

From the above results, it could be concluded that the simultaneous incorporation of sodium metabisulphite as an antioxidant and potassium dihydrogen phosphate as a microenvironmental pH adjuster could be a potential approach for enhancing the stability of sildenafil citrate in its formulations. In addition, the suggested formula could be an effective promising

tablet formulation for the drug with rapid disintegration characteristics and enhanced physical and chemical stability.

Table 1: Factors and levels used for the 2^2 factorial design of sildenafil citrate tablet formulations.

Factor	Levels	
	+	-
Filler Type (A)	Avicel PH 102	Spray-dried lactose
Disintegrant type (B)	Ac-Di-Sol	Explotab

Table 2: Composition of different sildenafil citrate rapidly disintegrating tablets prepared according to the experimental design used.

Ingredient (mg/tablet)	Formulation			
	(1)	a	b	ab
Sildenafil citrate	70 mg	70 mg	70 mg	70 mg
Avicel PH 102	_	313.6 mg	_	313.6 mg
Spray-dried lactose	313.6 mg	_	313.6 mg	_
Ac-Di-Sol	_	_	8 mg	8 mg
Explotab	8 mg	8 mg	_	_
Mg stearate	4 mg	4 mg	4 mg	4 mg
Sodium metabisulphite	0.4 mg	0.4 mg	0.4 mg	0.4 mg
KH_2PO_4	4 mg	4 mg	4 mg	4 mg

Table 3: Saturated solution pH of different acidic compounds.

Acidic compound	***Saturated solution pH****
Citric acid anhydrous	2.100 ± (0.016)
Fumaric acid	2.480 ± (0.011)
Monosodium citrate	3.760 ± (0.021)
Potassium dihydrogen phosphate (Monobasic potassium phosphate)	4.380 ± (0.0130

* Mean ± (SD).

Table 4: Effect of different acidic compounds on the microenvironmental pH of sildenafil citrate rapidly disintegrating tablet blends.

Formulation	Microenvironmental pH in presence of 1% of the following acidic compounds*				
	Nil	potassium dihydrogen phosphate	monosodium citrate	fumaric acid	citric acid
F (1)	6.81 ± (0.046)	4.51 ± (0.031)	3.78 ± (0.041)	2.54 ± (0.021)	2.29 ± (0.032)
F a	5.77 ± (0.033)	4.39 ± (0.028)	3.71 ± (0.028)	2.46 ± (0.025)	2.21 ± (0.042)
F b	6.84 ± (0.029)	4.47 ± (0.033)	3.76 ± (0.014)	2.52 ± (0.018)	2.26 ± (0.021)
F ab	5.79 ± (0.057)	4.41 ± (0.038)	3.75 ± (0.019)	2.49 ± (0.022)	2.22 ± (0.025)

* Mean ± (SD).

Table 5: Mean physical properties of sildenafil citrate/adjuvants powder blends used for the preparation of different rapidly disintegrating tablet formulae.

Formula	Tapped bulk density (g/ml)	Carr's index	Hausner ratio	Angle of repose (θ)
Pure drug	0.556	15.911	1.445	41.64
F(1)	0.732	17.896	1.220	34.61
F a	0.469	20.042	1.250	35.03
F b	0.750	18.367	1.225	34.14
F ab	0.461	21.687	1.277	34.45

Table. 6. Characterization of different sildenafil citrate rapidly disintegrating tablet formulae.

Formula	Average weight (mg) ± S.D.	Average drug content (%) ± S.D.	Friability (%)	Hardness (Kg) ± S.D.	Average disintegration time (sec.) ± S.D.	Percent drug dissolved after 10 minutes DP_{10} (%)
F(1)	400.09 ± 1.12	98.143 ± 0.272	0.161	8.250 ± 0.485	22.000 ± 0.990	87.41 ± 1.89
F a	399.91 ± 1.90	97.497 ± 0.552	0.088	6.500 ± 0.424	12.000 ± 1.414	86.33 ± 2.15
F b	399.97 ± 1.02	96.933 ± 0.621	0.136	8.750 ± 0.354	18.000 ± 2.121	85.55 ± 2.84
F ab	400.06 ± 1.34	96.003 ± 0.331	0.072	7.000 ± 0.707	10.000 ± 1.131	82.60 ± 1.55

Table 7: Effect of storage at 50 °C / 75 % R.H. for twelve weeks on the hardness, disintegration and percent drug dissolved after 10 minutes of F b and F ab sildenafil citrate rapidly disintegrating tablets*.

Formula	Hardness(Kg)	Disintegration time(min.)	DP_{10}(%)
F b	4.50 ±(0.32)	40 ±(1.54)	81.22 ±(2.31)
F ab	8.00 ±(0.56)	45 ±(2.27)	76.06 ±(1.88)

* Mean ± (SD

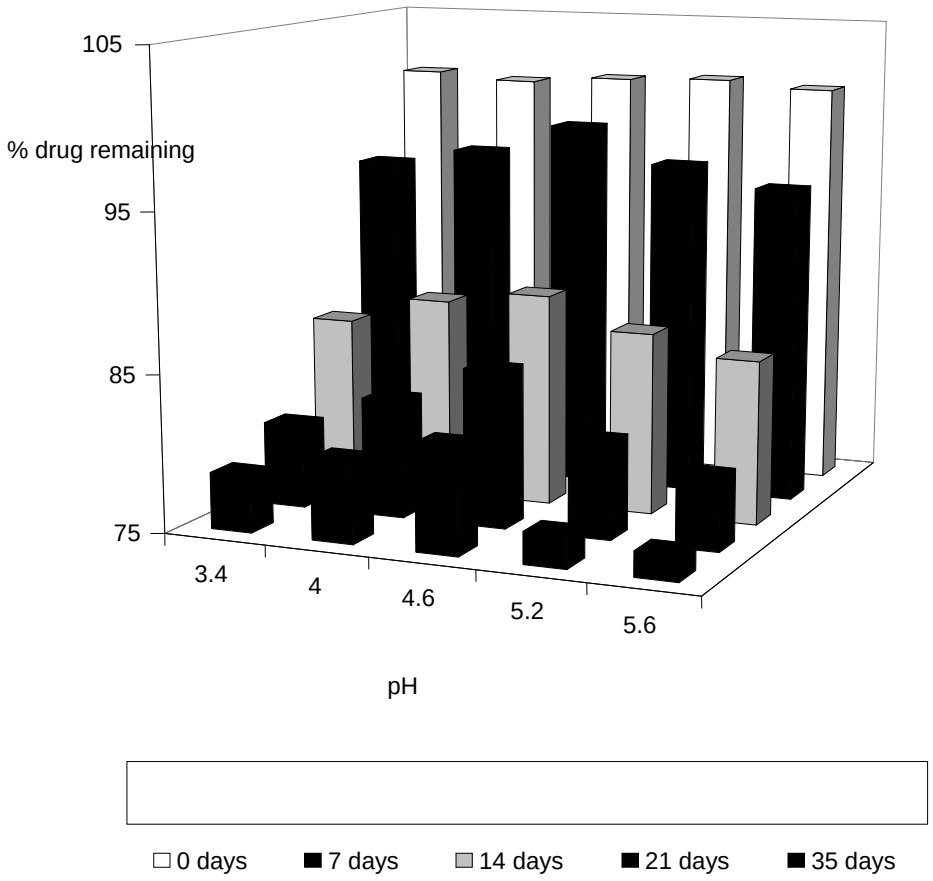

Fig. 1. Effect of pH on the stability of sildenafil citrate saturated solutions (McIlvaine buffer) after storage at 60°C for 35 days.

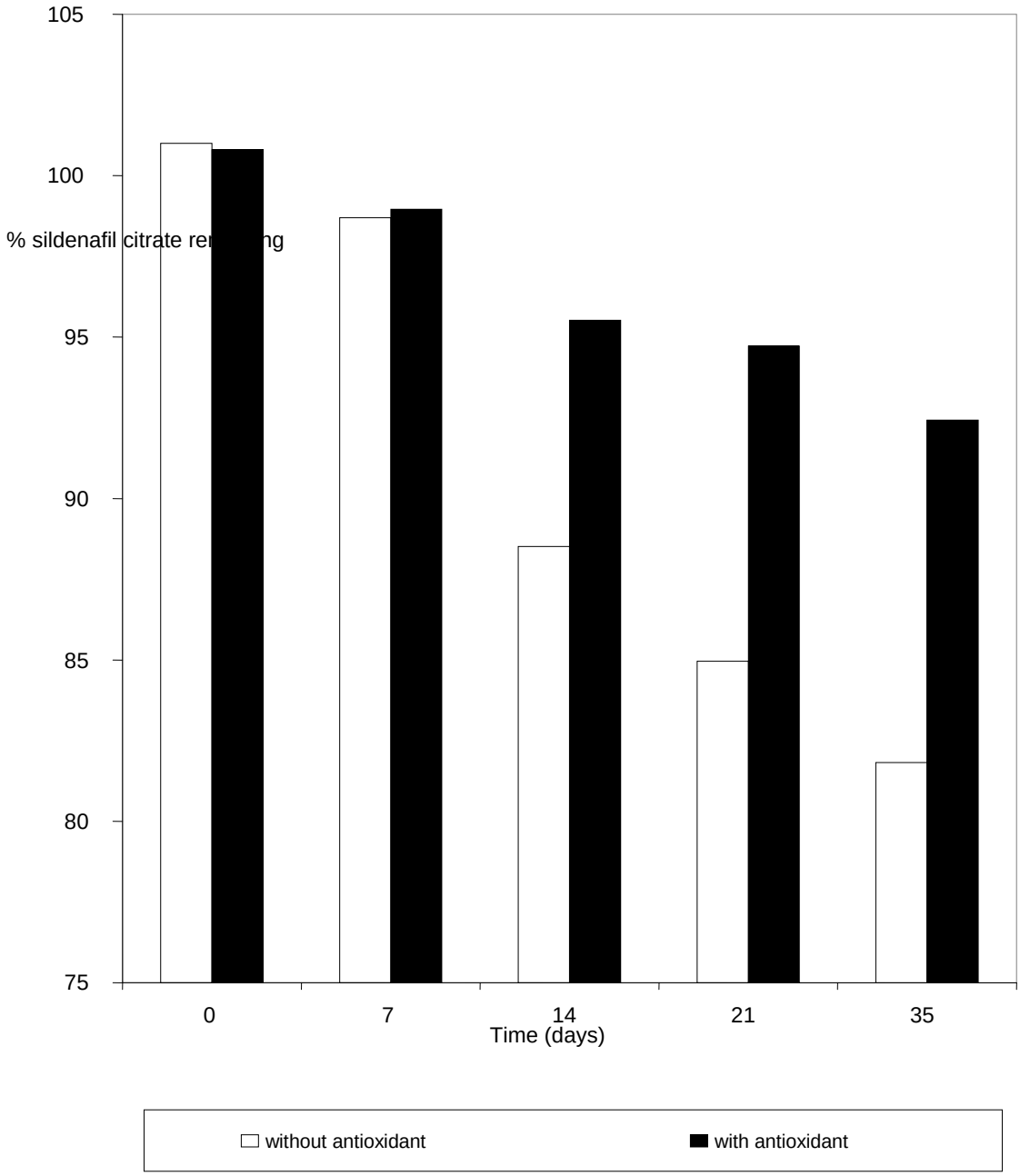

Fig. 2. Effect of using 0.1% w/v sodium metabisulphite as an antioxidant on the stability of sildenafil citrate saturated solution in McIlvaine buffer (pH 4.6)..

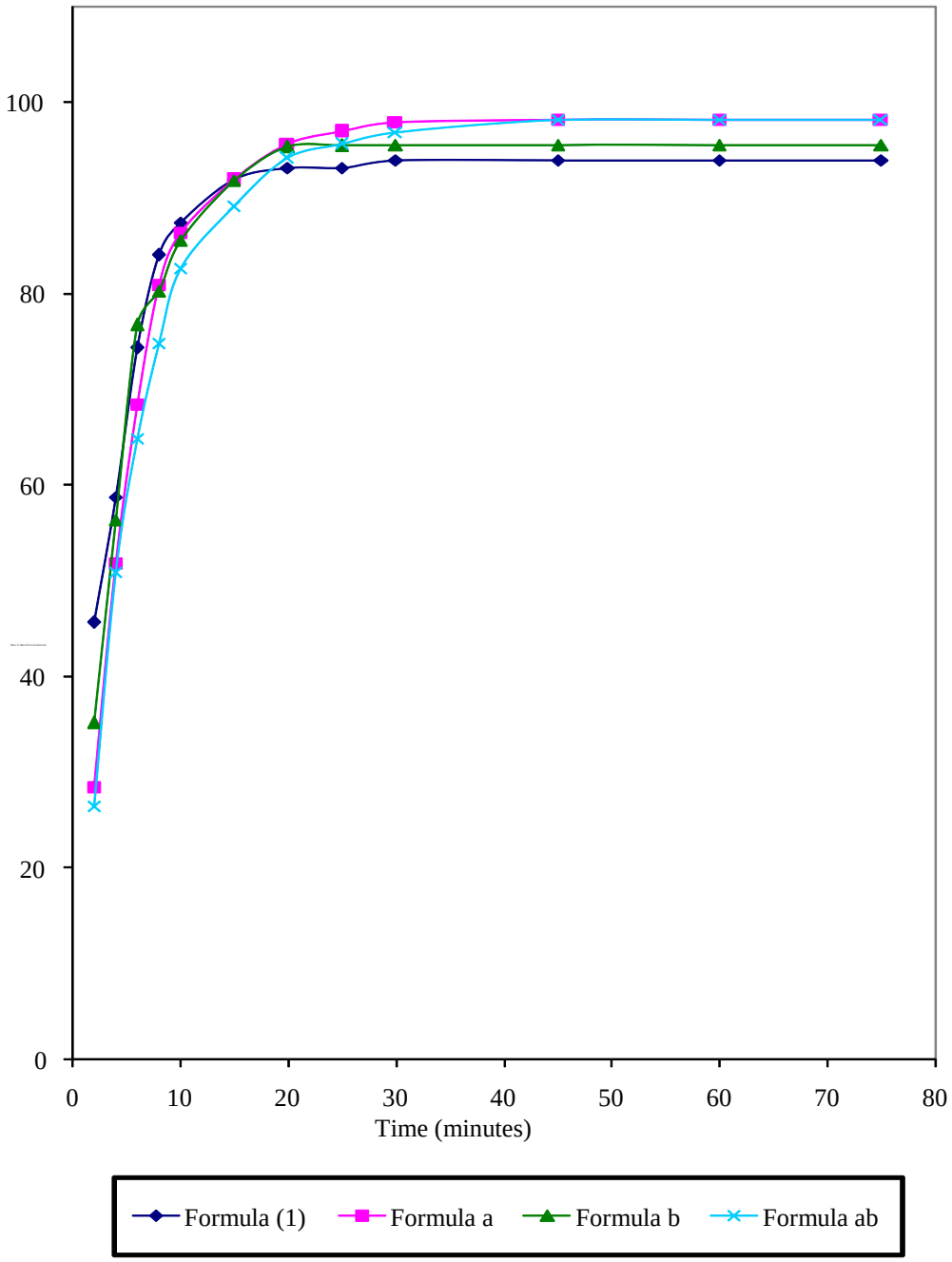

Fig. 3: Dissolution of sildenafil citrate from its rapidly disintegrating tablet formulae in 0.1 N HCl

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