Selection of the best solvent and pH indicator for the acid-base titration of indomethacin in laboratories for pharmacy college students

Luma A. Musa[a] a Department of Pharmaceutical Chemistry, College of Pharmacy, Mustansiriyah University, Baghdad, Iraq. lumaamer@uomustansiriyah.edu.iq

Hussien A. Karim [a] a Department of Pharmaceutical Chemistry, College of Pharmacy, Mustansiriyah University, Baghdad, Iraq. hussienak@uomustansiriyah.edu.iq

Ahmed M. Ahmed[a] a Department of Pharmaceutical Chemistry, College of Pharmacy, Mustansiriyah University, Baghdad, Iraq. ahmed-mazin@uomustansiriyah.edu.iq

ABSTRACT

Objective: To test a number of solvents and pH indicators in the acid-base titration of indomethacin drug and select the best ones of them that will give the best results than the usual solvent and indicator used in the designed acid-base titration of indomethacin.
Methods: A series of solvents and pH indicators was tested in the acid-base titration assay of indomethacin.
Results: one of the tested compounds give better result than these used in usual method of acid-base titration of indomethacin.
Conclusion: The most tested solvents and indicators show results comparable to that of the usual solvent and indicator used in the usual method of acid-base titration designed for indomethacin only thymol blue indicator give color change at the end point that is more distinguishable than the usual used indicator.

Keywords: Acid-Base Titration, Indomethacin, Ph Indicators, Anti-Inflammatory Activity

Introduction:

Acid base titration is laboratory method used for quantitative determination of the concentration of an acid or base by neutralization it with standard solution of acid or base with known concentration.[1,2,3,4] usually we use pH indicator to monitor the progression of the reaction (show color change at the endpoint) and is considered a neutralization reaction called alkalimetery (determination of the concentration of base by using acid) or acidimetery (determination of the

because of its low boiling point 56 C° [15] and the change in color at the end point is not so clear to be noticed (the change in color from pale yellow to very slightly pink).The phenolphthalein color change from colorless at acidic pH to pink at basic pH.[16] The decision was made to test another concentration of acid by using base) . [5,6]

Indomethacin is non-steroidal anti-inflammatory drug (NSAID).[7] it is non-selective cyclooxygenase (COX) enzyme inhibitor that inhibit both COX-1 and COX-2 isoforms .[8] indomethacin inhibit the biosynthesis of prostaglandins which have an important inflammatory roles in inflammation.[9,10]

this drug use in the therapy of conditions like ; rheumatoid arthritis , osteoarthritis, gouty arthritis [11] and also for headache [12].indomethacin is acid and it's derived from acetic acid.[13] The usual acid base titration used for determination of indomethacin concentration in capsule use acetone as solvent and phenolphthalein as pH indicator,[14] but because of the hot weather in Iraq and some other countries the acetone will readily volatile solvents, these solvent must be readily available, miscible with water and have higher boiling point than acetone.

Also testing other pH indicators to see the change in color at the end point. The tested solvents were :

1- Methanol (is simple aliphatic alcohol termed methyl alcohol or carbinol used as solvent or raw material in chemical industry its boiling point 65 C°). [17]
2- Ethanol (is aliphatic alcohol used as organic solvent and intermediate in the production of other chemicals has boiling point 78 C°). [18]
3- 1-propanol (aliphatic alcohol also called propyl alcohol its boiling point 97 C°). [19]
4- Tetrahydrofuran THF (colorless liquid its boiling point 66 C°). [20]

The selected pH indicators were (methyl orange, methyl red, phenol red and thymol blue).

The tested indicators were :

1- Thymol blue; the color changes from red to yellow in acidic medium and from yellow to blue in alkaline medium. [21]
2- Phenol red; the color changes from yellow (at pH 6) to pink (at pH 8).[22]
3- Methyl red; the color changes from red (at pH 4.4) to yellow (at pH 6.2).[23]
4- Methyl orange; the color changes from red (pH below 3.1) to yellow (pH above 4.4).[24]

Materials and Methods:

All reagents and solvents were of analytical type and generally used as received from the commercial suppliers (Reidel-DeHaen, Germany, Himedia,India, Rubilabor chemical , Spain and BDH, England). indomethacin was supplied by the Shanghai Renyoung Company, China.

General procedures for the titration[14] :

1- Put 25 mg of indomethacin in conical flask.
2- Fill the burette with 0.01 N NaOH.
3- Add 15 ml of the solvent and three drops of the indicator on flask of indomethacin.
4- Titrate the flask of indomethacin with NaOH until reach the end point which detected by the first stable change in the color of the solution in the flask.

Results and discussion :

The weight of the indomethacin in the solution of the flask calculated by the following equation :

$$wt\ of\ indomethacin = VB * NB * EQ.WT$$

Where VB is volume of NaOH at the endpoint (which must be 7ml to give the correct weight of indomethacin in flask)

NB is the normality of NaOH in the burette.

$EQ.WT$ equivalent weight of indomethacin (557.8g/mol)

For each solvent and indicator tested the experiment repeated 6 times to ensure the result and each run give the same result for particular solvent and particular indicator.

Table 1: the color change for the tested indicators by using acetone as solvent ;

Indicator used	Color of the solution at start point	Color of the solution at end point	The volume to reach the end point
Phenolphthalein	Pale yellow	Very slight pink	7ml

Mmethyl orange	yellow	yellow	After 16ml
Phenol red	yellow	pink	9ml
Methyl red	yellow	orange	8.6ml
Thymol blue	yellow	Greenish blue	7ml

Table 2: the volume of endpoint by using thymol blue indicator and different solvents:

Solvent used	**Volume to reach the end point**
acetone	7ml
methanol	7.8ml
ethanol	7.6ml
1-propanol	7.8ml
tetrahydrofuran	8ml

Figure 1: the color change for the indicators at the endpoint.

As the tables and the figure shows that the best color change at the accurate endpoint is for the thymol blue indicator and the best solvent that give the accurate endpoint is acetone.

So the procedure must change to use thymol blue indicator instead of phenolphthalein indicator.

Conclusion :

1- The solvents and indicators are tested successfully.
2- The procedure repeated for each of the tested solvents and indicators 6 times at the same conditions to make assurance of the results.
3- The procedures assigned for titration of indomethacin in laboratories must changes to include the thymol blue indicator instead of phenolphthalein and keeping acetone solvent to give the best results.

Acknowledgments:
The authors are greatly thankful to management and principal, Department of Pharmaceutical Chemistry/ College of Pharmacy/ Mustansiriyah University for their help and support.

References:

1. Kahlert H, Meyer G, Albrecht A. Colour maps of acid–base titrations with colour indicators: how to choose the appropriate indicator and how to estimate the systematic titration errors. ChemTexts. 2016 Jun;2(2):1-28.
2. Azevedo MC, Cavaleiro AM. The acid–base titration of a very weak acid: boric acid. Journal of chemical education. 2012 May 8;89(6):767-70.
3. Pierre D. Acid-Base Titration. Undergraduate Journal of Mathematical Modeling: One+ Two. 2019;10(1):8.
4. Gordon WE. Data analysis for acid-base titration of an unknown solution. Analytical Chemistry. 1982 Aug 1;54(9):1595-601.
5. Zulfajri M. Activity analysis of anthocyanin from Syzygium cumini (L.) skeels as a natural indicator in acid-base titration. Rasāyan Journal of Chemistry. 2018;11(1):135-41.
6. Hipi D, Daud EP, Soga GD. IDENTIFICATION OF ALKALIMETRIC LEVELS USING ACID-BASE REACTION PRINCIPLES. Journal of Health, Technology and Science (JHTS). 2021;2(4):11-20.
7. Levenick JM, Gordon SR, Fadden LL, Levy LC, Rockacy MJ, Hyder SM, Lacy BE, Bensen SP, Parr DD, Gardner TB. Rectal indomethacin does not prevent post-ERCP pancreatitis in consecutive patients. Gastroenterology. 2016 Apr 1;150(4):911-7.
8. Marinella MA. Indomethacin and resveratrol as potential treatment adjuncts for SARS-CoV-2/COVID-19. International journal of clinical practice. 2020 Sep;74(9):e13535.
9. Bindu S, Mazumder S, Bandyopadhyay U. Non-steroidal anti-inflammatory drugs (NSAIDs) and organ damage: A current perspective. Biochemical pharmacology. 2020 Oct 1;180:114147.
10. Al-Matary A, Shaheen AA, Abozaid S. Use of Prophylactic Indomethacin in Preterm Infants: A Systematic Review and Meta-Analysis. Frontiers in pediatrics. 2022 Apr 7;10:760029.
11. Shekhar N, Kaur H, Sarma P, Prakash A, Medhi B. Indomethacin: An exploratory study of antiviral mechanism and host-pathogen interaction in COVID-19. Expert review of anti-infective therapy. 2022 Mar 4;20(3):383-90.
12. VanderPluym J. Indomethacin-responsive headaches. Current neurology and neuroscience reports. 2015 Feb;15(2):1-8.
13. Lucas S. The pharmacology of indomethacin. Headache: The Journal of Head and Face Pain. 2016 Feb;56(2):436-46.
14. Assay of drugs.In:Ashutosh kar (Ed).pharmaceutical drug analysis.2nd edithion.New Delhi:New age international publishers.2005.p98-101.
15. Radwan A, Ookawara S, Mori S, Ahmed M. Uniform cooling for concentrator photovoltaic cells and electronic chips by forced convective boiling in 3D-printed monolithic double-layer microchannel heat sink. Energy

conversion and management. 2018 Jun 15;166:356-71.
16. Kiskan B, Antonietti M, Weber J. Teaching new tricks to an old indicator: pH-switchable, photoactive microporous polymer networks from phenolphthalein with tunable CO2 adsorption power. Macromolecules. 2012 Feb 14;45(3):1356-61.
17. Ott J, Gronemann V, Pontzen F, Fiedler E, Grossmann G, Kersebohm DB, Weiss G, Witte C. Methanol. Ullmann's encyclopedia of industrial chemistry. 2000 Jun 15.
18. Logsdon JE. Ethanol. Kirk-Othmer Encyclopedia of Chemical Technology. 2000 Dec 4.
19. Falbe J, Bahrmann H, Lipps W, Mayer D, Frey GD. Alcohols, aliphatic. Ullmann's encyclopedia of industrial chemistry. 2013;2:19-47.
20. Dannan GA. Tetrahydrofuran. Hamilton & Hardy's Industrial Toxicology. 2015 Mar 25:719-26.
21. Shimada T, Tochinai K, Hasegawa T. Determination of pH dependent structures of thymol blue revealed by cooperative analytical method of quantum chemistry and multivariate analysis of electronic absorption spectra. Bulletin of the Chemical Society of Japan. 2019 Oct 15;92(10):1759-66.
22. Wang E, Chow KF, Wang W, Wong C, Yee C, Persad A, Mann J, Bocarsly A. Optical sensing of HCl with phenol red doped sol–gels. Analytica chimica acta. 2005 Apr 8;534(2):301-6.
23. Ran R, Wang L, Su Y, He S, He B, Li C, Wang C, Liu Y, Chen S. Preparation of pH-indicator films based on soy protein isolate/bromothymol blue and methyl red for monitoring fresh-cut apple freshness. Journal of Food Science. 2021 Oct;86(10):4594-610.
24. Pirsa S, Karimi Sani I, Khodayvandi S. Design and fabrication of starch-nano clay composite films loaded with methyl orange and bromocresol green for determination of spoilage in milk package. Polymers for Advanced Technologies. 2018 Nov;29(11):2750-8.