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ORIGINAL ARTICLE

SOLUBILITY ENHANCEMENT OF PIROXICAM USING DIFFERENT CONCENTRATIONS OF THE HYDROTROPIC AGENT SODIUM BENZOATE

Rasha Khalid Dhahir

Department of Pharmaceutics, College of Pharmacy, University of Mosul, Mosul, Iraq

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Summary

Background: Piroxicam is a non-steroidal anti-inflammatory drug, used to alleviate inflammatory signs and symptoms. It is a potent acidic drug that presents mainly in unionized form in the stomach, thus it has a high permeability through the stomach, but poor aqueous solubility. This study, tried to explore the application of hydrotropes to improve the solubility of piroxicam by using different concentrations of the hydrotropic agent sodium benzoate.
Methods: Maximum absorbance of piroxicam and its calibration curve was determined using methanol as a solvent, saturated solubility of piroxicam in distilled water and in various concentrations of sodium benzoate 5%, 10%, 15% was measured.
Results: The results showed that saturated solubility of piroxicam in aqueous solutions of 5%, 10%, and 15% of sodium benzoate was 19, 53, and 89 time respectively greater than its solubility in distilled water.
Conclusion: There was a clear improvement in the solubility of piroxicam with the addition of the hydrotropic agent sodium benzoate, and that solubility increased with more increase in the concentration of the hydrotropic agent.

Key words: Piroxicam; Improvement in the solubility; Hydrotropes; Sodium benzoate

Introduction

Piroxicam belongs to the oxicam group of nonsteroidal anti-inflammatory drugs; with chemical structure of 4-hydroxy, -2-methyl-N-2-pyredenyl-2H-1, 2-benzothiazine-3-carboxamide 1, 1-dioxide (Figure 1). It is indicated for the reduction of the symptoms of osteoarthritis and rheumatoid arthritis. The drug is regarded as a potent acid; therefore, it remains as unionized form in the acidic medium of the stomach, and this is why it can penetrate the gastric membrane easily but cannot enter the systemic circulation. Thus the drug can be classified according to the Biopharmaceutics Classification System into a class-II, that characterized by high permeability, low solubility, as a result, solubility of piroxicam is the rate limiting step for its absorption (1, 2, 3).

Solubility enhancement of different poorly soluble compounds can be regarded as an obstacle that faces researchers and scientists in pharmaceutics, 40% of the active new chemical entities are poorly water soluble. There

✉ University of Mosul, College of Pharmacy, Department of Pharmaceutics, Mosul, Iraq
Rasha.kh@uomosul.edu.iq

are many techniques being employed to improve the solubility of the compounds (4, 5). Bioavailability, efficacy, and undesirable effect could be improved by improving solubility of the drug in different dosage forms (5, 6). Solubilization process involves breakage of the inter-ionic or intermolecular bond of the solutes and the construction of anther bonds with the molecules or ions of the solvent. Any additives or salts that increase the amount of the drug dissolved in a given solvent result in salting in, and the reverse result in salting out (4, 6). These salts lead to salting in are refereed as hydrotropic salts, and the phenomenon are referred as hydrotropism. The phenomenon of hydrotropism involves the formation of a complex between hydrotropic agents like sodium benzoate, sodium alginate, sodium acetate, and urea, with the poorly soluble drugs rather than the formation of a colloidal solution (4, 5, 6).

Therefore, solubility of a sparingly soluble solute can be improved by the application of such hydrotropic technique, in which the added hydrotropic agent can improve the aqueous solubility of the drug under normal conditions; due to the formation of regular gatherings of hydrotropic molecules at critical concentration (7). Hydrotropism can be defined as a solubilization phenomenon, in literatures, this term refers to non-micelles forming substances, that may be liquids, solids, organic or inorganic compounds. It depends on the fact that the aqueous solubility of a drug can be improved by the addition of a large amounts of a second solute (4). This method of solubility improvement is superior to other solubilization technique since it is independent on pH, does not require emulsification , has a high selectivity, and there is no need for organic solvent (8).

Hydrotropes in general are surface-active, water-soluble compounds that can improve the solubility of organic solutes such as acids, aldehydes, ketones, alcohols, esters, fats, and hydrocarbons. Neuberg's hydrotropic salts are composed mainly of two essential parts; anionic group that participates in high aqueous solubility and hydrophobic aromatic ring that involves in the mechanism of hydrotropic solubilization (4).

Hydrotrope is composed of hydrophobic and hydrophilic parts, but the size of the hydrophobic part is not enough to form spontaneous aggregation, that means it doesn't have critical concentration above which spontaneous aggregation occur. Hydrotrope is composed of anionic group than involved in bringing of the aqueous solubility, and hydrophobic aromatic ring that contributes with its planner structure, in hydrotopic solubilization, two important mechanisms are involved in aromatic hydrotropes such as sodium salicylate, and nicotinamide, one is stacking complexation, and the other is self-aggregation (8).

Hydrotropic solubilization technique has many applications in pharmaceutics, since it can be used for quantitative estimations of poorly water-soluble drugs, regression equations for drugs, spectrophotometric analysis of a drug in marketed tablet formulations, and preparation of topical solutions and injections of poorly water-soluble drugs. It can also be used as permeation enhancers, for producing fast release preparations, and for nanotechnology (9, 10).

The aim of this study is to enhance the solubility of piroxicam by using different concentrations of the hydrotropic agent, sodium benzoate.

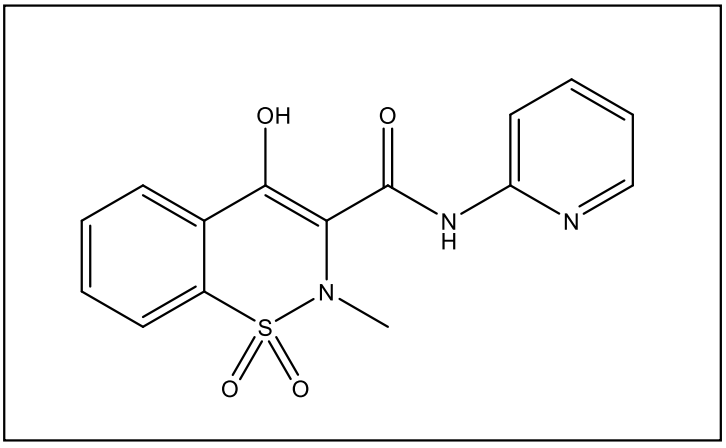

Figure 1. Chemical structure of piroxicam.

Materials and Methods

Determination of maximum absorbance of piroxicam and calibration curve:

A stuck solution of piroxicam in methanol (100 µg/ml) was prepared by precisely weighing 10 mg of the drug in 25 ml beaker then adding 10 ml methanol with continuous stirring until the drug is completely dissolved and transferred to 100-ml volumetric flask, 50 ml of methanol was added with a continuous shaking. Finally, the volume is completed with methanol to 100 ml. Piroxicam solution of 10 µg/ml was prepared by diluting of the stock solution of 100 µg/ml with methanol, the solution was taken in a quartz cell and scanned by UV-spectrophotometer (Specord 40, analytic Jena) at a wavelength ranging from 200-400 nm using methanol as a blank, λ_{max} of piroxicam was determined. From the freshly prepared stuck, series of diluted samples were prepared and measured at 227.7 nm wavelength, using methanol as a blank, calibration curve of piroxicam was plotted (11).

Solubility analysis of piroxicam in distilled water and in various concentrations of the hydrotropic agent sodium benzoate:

Piroxicam was added in an excess amount to 20 ml of distilled water, and to the aqueous solutions of the hydrotropic agent sodium benzoate in three different concentrations 5%, 10%, and 15%, to make saturated solution of each. The solutions were stirred for 30 min, then kept for 24 hr at 25 °C. Each solution was filtered through filter paper (Whatman 41), the absorbance of each clear solution was measured using UV-spectrophotometer at 227.7 wavelength to determine the amount of the drug dissolved.

Results

Determination of maximum absorbance of piroxicam and calibration curve

The diluted solution of piroxicam (10 µg/ml) in methanol was scanned by UV spectrophotometer at a wavelength of 200-400 nm using 1 cm quartz cell. The result was a spectrum with maximum absorbance (λ_{max}) of 227.7. The calibration curve of piroxicam in methanol was constructed by UV analysis at 227.7 nm. By plotting the absorbance versus concentration, a straight line was obtained, the R-squared value was 0.9981, and the linearity limit was from 1-12 µg/ml as shown in Figures 2.

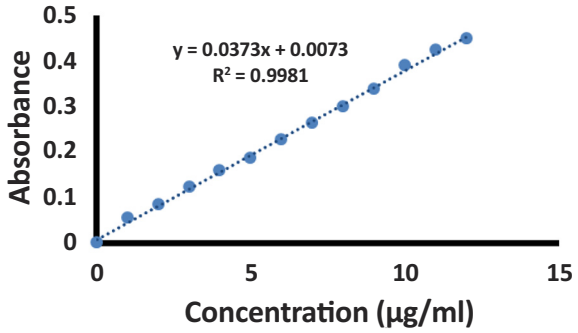

Figure 2. Calibration curve of piroxicam.

Solubility analysis of piroxicam in distilled water and in various concentrations of the hydrotropic agent sodium benzoate

UV-spectrophotometric analysis of piroxicam in its saturated solution of distilled water and in aqueous solutions of different concentrations of sodium benzoate is shown in Table 1, whereas solubility of piroxicam in distilled water and in different concentrations of aqueous solution of sodium benzoate is shown in Table 2. The results indicated that there are significant differences ($p<0.05$) between solubility of piroxicam in distilled water and in different concentrations of sodium benzoate in aqueous solution. The aqueous solubility of piroxicam in µg/ml as a function of sodium benzoate concentration in gram/100 ml is shown in Figure 3.

Table 1. UV-spectrophotometric analysis of piroxicam in its saturated solution of distilled water and in aqueous solutions of different concentrations of sodium benzoate.

Type of the saturated solution	Absorbance	Dilution factor
Distilled water	0.06	10
5% sodium benzoate	0.06	200
10% sodium benzoate	0.147	200
15% sodium benzoate	0.241	200

Table 2. Solubility of piroxicam in distilled water and in different concentrations of aqueous solution of sodium benzoate.

Type of the medium	Drug solubility in µg/ml
Distilled water	14.128
5% sodium benzoate	282.5
10% sodium benzoate	749.06
15% sodium benzoate	1253.08

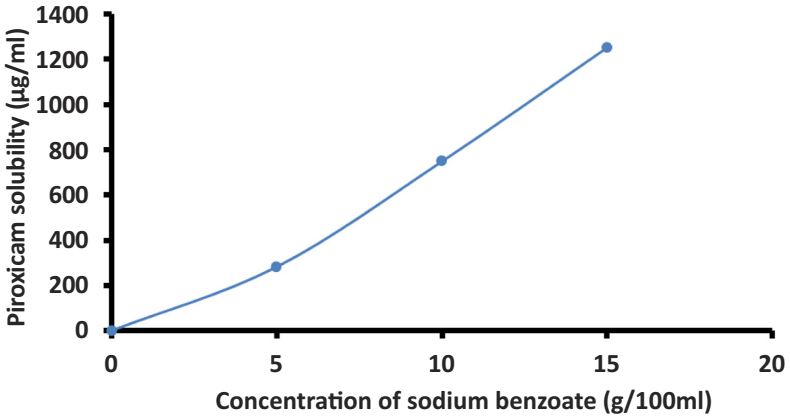

Figure 3. Aqueous solubility of piroxicam in µg /ml as a function of sodium benzoate concentration in gram/100 ml.

Discussion

Hydrotropism is a phenomenon in which the solubility of a sparingly soluble drug is improved in the aqueous medium when excess amount of a second solute is added (12). Various of such agents are available for improving the solubility of a poorly soluble drug such as sodium acetate, sodium benzoate, sodium salicylate, sodium toluate, and sodium toluene sulfonate. In this experiment sodium benzoate hydrotropic agent was applied for improving the solubility of piroxicam, it showed a significant enhancement in the solubility of the drug at room temperature (13).

Saturated solubility of piroxicam in 5% sodium benzoate was 282.5 µg/ml which was 19-time greater than its saturated solubility in distilled water which was about 14.128 µg/ml, there is a significant difference in solubility ($p<0.05$). While the saturated solubility of the drug in 10% sodium benzoate was 749.06 µg/ml which means that there is about 53-time improvement of its solubility in comparison to that in distilled water ($p<0.05$). Finally, the solubility of the drug in 15% sodium benzoate was 1253.08 µg/ml, which is about 89-time greater than it is solubility in aqueous solution ($p<0.05$). This indicated that there was an increase in the solubility of piroxicam with the increase in sodium benzoate concentration, they were in compliance with the results obtained by Ibrahim *et al*. (2020), who studied the effect of different concentrations and types of hydrotropic agents on the solubility of nimodipine (14). Also these results were in accordance with those obtained by El-Houssieny *et al*. (2014), who tried

to enhance the dissolution rate and solubility of dexibuprofen in aqueous medium by mixed hydrotropic solubilization technique (15), and with Raghunath and Sagde (2021) who used individual and mixed hydrotropic agents in different concentrations and types to improve the solubility of piroxicam (16), also with Mansuk *et al*. (2020) who formulated a fast-dissolving oral dosage form of piroxicam, to provide quick onset of action by using mixed solvency, the solubility of the drug was examined in different types of hydrotropic agents, and the highest results were obtained with 40% sodium benzoate (17) and with Carpenter G. (2018), who tried to formulate and develop a fast-dissolving oral film of piroxicam with enhanced drug loading utilizing mixed-solvency concept (18).

Conclusion

Majority of the chemical agents that are being discovered are of poor aqueous solubility, therefore many attempts have been adapted to improve their solubility and bioavailability. From different studies, hydrotropic solubilization can be regarded as an excellent approach to solubilize poorly soluble drugs. In this research, piroxicam solubility showed a dramatic improvement by the hydrotropic agent sodium benzoate when compared to its solubility in distilled water. With increasing the concentration of this hydrotropic agent, the solubility of the drug also increased.

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Conflict of interest

The authors declare no conflict of interest concerned in the present study.

Adherence to Ethical Standards

Not applicable. *In vitro* solubility study.

Reference

1. Xu S, Rouzer CA, Marnett LJ. Oxicams, a class of nonsteroidal anti-inflammatory drugs and beyond. IUBMB life. 2014;66(12):803-811. https://doi.org/10.1002/iub.1334
2. Xu S, Hermanson DJ, Banerjee S, et al. Oxicams bind in a novel mode to the cyclooxygenase active site via a two-water-mediated H-bonding network. Journal of Biological Chemistry. 2014;289(10):6799-6808. https://doi.org/10.1074/jbc.M113.517987
3. Dhahir RK, Al-Kotaji MY. Formulation of orally disintegrating tablets of cinnarizine by using direct compression method. Int J Appl Pharm. 2019;11(1):117-123. https://doi.org/10.22159/ijap.2019v11i1.29599
4. Nidhi K, Indrajeet S, Khushboo M, et al. Hydrotropy: A promising tool for solubility enhancement: A review. International Journal of Drug Development and Research. 2011;3(2):26-33.
5. Gandhi NN, Kumar MD, Sathyamurthy N. Effect of hydrotropes on solubility and mass-transfer coefficient of butyl acetate. Journal of Chemical & Engineering Data. 1998;43(5):695-9. https://doi.org/10.1021/je970212k
6. Coffman RE, Kildsig DO. Hydrotropic solubilization—mechanistic studies. Pharmaceutical research. 1996;13(10):1460-1463. https://doi.org/10.1023/A:1016011125302
7. Rodríguez A, Graciani MD, Moyá ML. Effects of addition of polar organic solvents on micellization. Langmuir. 2008;24(22):12785-12792. https://doi.org/10.1021/la802320s
8. Kumar VS, Raja C, Jayakumar C. A review on solubility enhancement using hydrotropic phenomena. Int. J. Pharm. Pharm. Sci. 2014;6(6):1-7.
9. Dhapte V, Mehta P. Advances in hydrotropic solutions: An updated review. St. Petersburg Polytechnical University Journal: Physics and Mathematics. 2015;1(4):424-35. https://doi.org/10.1016/j.spjpm.2015.12.006
10. Dhahir RK, Al-Nima AM, Fadia AB. Nanoemulsions as Ophthalmic Drug Delivery Systems. Turkish Journal of Pharmaceutical Sciences. 2021;18(5):652. doi: 10.4274/tjps.galenos.2020.59319

11. Bachhav AA, Ahire SA, Jadhav AG. Preformulation study of piroxicam. International Journal of Pharmaceutical Sciences and Research. 2019;10:811-818. doi: 10.13040/ IJPSR.0975-8232.10(2).811-18.
12. Savjani KT, Gajjar AK, Savjani JK. Drug solubility: importance and enhancement techniques. International Scholarly Research Notices. 2012;2012.
13. Patel VF, Sarai J. Synergistic effect of hydrotrope and surfactant on solubility and dissolution of atorvastatin calcium: screening factorial design followed by ratio optimization. Indian Journal of Pharmaceutical Sciences. 2014;76(6):483.
14. Ibrahim NJ, Smail SS, Hussein NR, et al. Solubility enhancement of nimodipine using mixed hydrotropic solid dispersion technique. Zanco Journal of Medical Sciences (Zanco J Med Sci). 2020;24(3):386-394. https://doi.org/10.15218/zjms.2020.046
15. El-Houssieny BM, El-Dein EZ, El-Messiry HM. Enhancement of solubility of dexibuprofen applying mixed hydrotropic solubilization technique. Drug discoveries & therapeutics. 2014;8(4):178-184. https://doi.org/10.5582/ddt.2014.01019.
16. Raghunath JS, Jaiswal NR, Chavan GC, et al. Solubility Enhancement of Piroxicam by Mixed Hydrotropy Technique. 2021;10(8);1387-1419. https://doi.org/10.20959/wjpr20218-20984.
17. Mansuk AG, Deshmukh D, Maheshwari RK, et al. Formulation optimization and characterization of solid dispersion of piroxicam prepared by novel application of mixed solvency concept. Pharmaceutical Resonance. 2020;2(2):41-46.
18. Carpenter G. Formulation and Development of Fast Dissolving Oral Film of a Poorly Soluble Drug Piroxicam with Improved Drug Loading Using Mixed Solvency Concept and its Evaluation. Asian Journal of Pharmaceutics (AJP). 2018;12(03).