ISSN–2230-7346

Journal of Global Trends in Pharmaceutical Sciences

SYNCHRONOUS DETERMINATION OF PARACETAMOL AND DICLOFENAC SODIUM USING ACID TREATED LOCAL SYRIAN CLAY AS CHROMATOGRAPHIC SUPPORT INTLC – DENSITOMETRIC METHOD

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ARTICLE INFO

Key Words

Paracetamol, DiclofenacSodium, Acid treated local Syrian clay, Bentonite, Simultaneous Determination, TLC

Access this article online

Website: https://www.jgtps.com/

Quick Response Code:

ABSTRACT

A New Chromatographic Support,was prepared from acid treated Local SyrianClay (S .B_{AW}) and using it for preparing chromatographic thin layers (0.25 mm thickness) to separate and Synchronousdetermination of Paracetamol, and Diclofenac Sodium in pure form and in tablets. The separation carried out using mobile phase consisted of Ethylacetate:methanol:ammonia solution (55 :5 :3) v/v. The specific surface area of Acid treated Local Syrian Clay,was 91m^2/g. Quantification was carried out densitometerically, atλ = 250 nm for Paracetamol,and at λ = 290 nm for Diclofenac Sodium. The retardation factors (R_f) of Sodium Diclofenac, and Paracetamol, were 0.35, and 0.84 respectively. Calibration curves were obtained in the ranges of 5.0-40.0 µg/spot, and 2.0-16.0 µg/spot for standard solutions of Paracetamol, and Diclofenac Sodium respectively.The New Prepared Chromatographic Thin Layers were successfully applied for analysis of commercial dosage forms (tablets) containing the drugs with average recovery 99.25 –101.20% with RSD not more than 4.97%.

INTRODUCTION

Local Syrian clay (Syrian Bentonite) is rocky clay , it is considered as a porous cheap material naturally occurring in Syria. Local Syrian clay (Syrian Bentonite) constituents were determined , and Silica represents the major constituent of clay, in addition to several amounts of other metallic oxides. Local Syrian clay (Syrian Bentonite) consists of 47% SiO_2, 14.4% Al_2O_3 and some other oxides as Fe_2O_3, MgO, CaO, Na_2O and others [1- 4]. Bentonite has large pore volumes and high specific surface area. The thermal treatment causes decreasing of its specific surface area with increasing in the temperature of thermal treatment , and prolonged washing of bentonite by 6 N HCI removes all soluble oxides and about 67% of total iron oxide from the adsorbent, causing decrease of specific surface area and hydrolysis of siloxane groups on the surface of the support to yield more silanol groups [1- 4]. Bentonite clays are used in many industrial products and processes, drilling fluids, certain lubricating grease [5], and it can be used as chromatographic supports in gas chromatography to separate different of chemical mixtures after grafting with different methods. Modification of the support surface by reaction with silanol groups was carried out by means of chlorosilane compounds as reactants, or by condensation of a suitable polymer as PEG-20M [6-10]. Bentonite is used

as stationary phase in thin layer chromatography to separate some metal ions, and some drugs mixtures [11-14].

Acetaminophen (Paracetamol): $C_8H_9NO_2$, Chemically it is N-(4hydroxyphenyl) acetamide (figure 1,a). It is the most commonly taken analgesic worldwide and is recommended as first-line therapy in pain conditions by the World Health Organization (WHO). It is also used for its antipyretic effects, helping to reduce fever. Acetaminophen is often found combined with other drugs in more than 600 over the counter (OTC) allergy medications, cold medications, sleep medications, pain relievers, and other products [15,16] .

Diclofenac Sodium: C14H10Cl2NNaO2 is a non-steroidal anti-inflammatory agent (NSAID) with antipyretic and analgesic actions. It is primarily available as the sodium salt. Chemically it is 2-{2-[(2,6dichlorophenyl)amino]phenyl}acetic acid (figure 1,b). It is used For the acute and chronic treatment of signs and symptoms of osteoarthritis and rheumatoid arthritis. The anti-inflammatory effects of diclofenacSodium are believed to be due to inhibition of both leukocyte migration and the enzyme cylooxygenase (COX-1 and COX-2), leading to the peripheral inhibition of prostaglandin synthesis. As prostaglandins sensitize pain receptors, inhibition of their synthesis is responsible for the analgesic effects of diclofenac. Antipyretic effects may be due to action on the hypothalamus, resulting in peripheral dilation, increased cutaneous blood flow, and subsequent heat dissipation [15-16]. The literature review described HPTLC, HPLC and UV-visible spectrophotometric method for determination of paracetamol [17-21]; HPTLC, HPLC, UV-visible spectrophotometry, Potentiometric titration method for diclofenac sodium [17,18,19, 22-27], The literature review described HPTLC, HPLC and UV-visible spectrophotometric method for simultaneous determination of paracetamol,and diclofenac sodium in combination with other drugs or with each other [28 - 43] . The aim of this study was to prepare a new chromatographic support from local Syrian clay by Acid Treated,**(S .B_{AW})**and using it in thin layer chromatography to develop, andvalidate analytical procedure for Synchronousdetermination of paracetamol, and diclofenac sodium in a tablet.The developed analytical procedure was successfully used for routine analysis of paracetamol, and diclofenac sodium in tablets dosage form without any interference from involved excipients.

2. MATERIALS AND METHODS:

2.1Apparatus: Specific Surface area was measured using a Spectrophotometric method depend on methylene Blue adsorption on JASCO V-650 dual beam UV-VIS spectrophotometer. Scanner-densitometer CS-9301PC (SHIMADZU) equipped with mercury, tungsten and deuterium lamps, CAMAG Hand Operated TLC Coater (Switzerland), CAMAG UV Cabinet for assessing and marking thin layer chromatograms under UV light (Switzerland), planetary ball mill, Vibration Sieves of size less than (20) µm (Germany) and different size of syringe (Hamilton, Switzerland) were used. Ultrasonic processor model POWERSONIC 405 (to sonicate the sample solutions) and electronic balance (Sartorius-2474; d=0.01 mg) were used.

2.2 Reagents and Materials: Paracetamol (99.5 %, ZIM Laboratories, Nagpur, India), and Diclofenac sodium (99.8%, ZIM Laboratories, Nagpur, India) were used. Methanol, Ethyl acetate, Strong ammonia solution, fluorescent indicator F254 for thin layer chromatography, Carboxymethylcellulose Sodium, and Concentrated Hydrochloric Acid,were of analytical grade, Merck, Germany. Water used was deionised and double distilled for Chemical and Pharmaceutical applications.

3. PROCEDURE:

3.1Preparation of stationary phase: Bentonite was crushed using a mortar and milled by planetary ball mill to obtain small pieces, which have diameter less than 20 µm, Further, the bentonite powder is activated with chemical reaction by Suspending 50 g of bentonite in 100 ml of HCl (6 M) for 24 hours, to remove soluble oxides especially iron oxide. The magnetic stirrer was employed to mix the solution at 300 rpm and temperature 85ºC. After that, the bentonite is washed several times using distilled water until the pH is neutral, and dried at 200 °C for 3 h, to obtained acid treated

Syrian Bentonite,. The yield chromatographic support named**(S .B_{AW})**

3.2 Preparation of TLC plates: For preparation of thin chromatographic layers, (10 g) of acid treated clay (acidic treated bentonite) was passed through a mesh vibrated sieves of size less than 20 µm, andthen it was mixed with (0.5 g) of fluorescence substance (F_{254}), then the mixture was added to 20 mL hot water containing (0.5 g) Carboxymethylcellulose Sodium as binder to obtain homogeneous slurry. The slurry was spread over glass plates (10×20 cm) by an CAMAG Hand Operated TLC Coater, to form uniform thin layer 0.25 mm thick. The plates were dried at 105 °C.

3.3 Mobile phase: Ethyl acetate: Methanol:ammonia solution (55:5:3)(v/v) were used for the development method as mobile phase.

3.4 Standard solutions: Stock solutionswere prepared by dissolving (2500 mg) of Paracetamol, and (1000 mg) of Diclofenac Sodium in 30 mL of methanol, then transferred into a 50 mL volumetric flask and the final volume was completed to 50 mL with the same solvent. Volumes 1, 2, 3, 4, 5,6,7 and 8 mL from the former solution were transferred into 10 mL volumetric flasks and completed to the mark with the same solvent methanol (these solutions contain: 5, 10 , 15 , 20 , 25,30, 35, and 40 $mg.mL^{-1}$, for Paracetamol , and 2 , 4 , 6, 8, 10,12, 14 and 16 $mg. mL^{-1}$, for Diclofenac Sodium).

3.5 Sample preparation: (DICLOGESIC) and (DICLOCIN) Each tablet of DICLOGESIC contains (500 mg Paracetamol , and 50 mg Diclofenac Sodium), and each tablet of DICLOCIN contains (250 mg Paracetamol , and 50 mg Diclofenac Sodium). Twenty tablets were weighed and the average tablet weight determined (each tablet contains: 500 mg , or 250 ofParacetamol, and 50 mg ofDiclofenac Sodium). The tablets were finely powdered and a portion of powder equivalent to the weight of one tablet was dissolved in 20 mL methanol and vigorously shaken for a 20 min on a mechanical shaker, then filtrated and transferred into a 25 mL volumetric flask and the final volume was completed to 25 mL with the same solvent. The solution for (DICLOGESIC tablet) contains: 20 mg/ml Paracetamol, and 2 mg/mlDiclofenac Sodium, and the solution for (DICLOCIN tablet) contains: 10 mg/ml Paracetamol, and 2 mg/ml Diclofenac Sodium).

4. PROCEDURE:

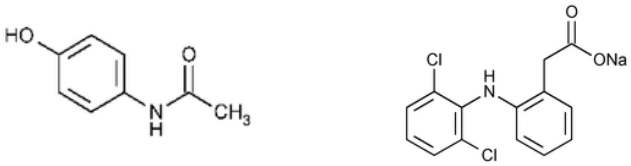
4.1 Chromatographic conditions: 1 µL of standard solutions were spotted on TLC glass plates (10 cm × 20 cm) pre-coated withacid treated bentonite (F_{254} with 0.25 mm thickness). Mobile phase was used for development method, then the plates were dried at room temperature and quantification was carried out densitometerically at λ = 250 nm for Paracetamol, and λ = 290 nm for Diclofenac Sodium. This process was repeated five times for each concentration and calibration curves were obtained in the range 5-40 µg/spot for Paracetamol, and in the range2-16 µg/spot for Diclofenac Sodium.

4.2 Pharmaceutical formulations: DICLOGESIC tablets contains 500 mg Paracetamol and 50 mg Diclofenac Sodium. DICLOCIN tablets contains 250 mg Paracetamol , and 50 mg Diclofenac Sodium. 1 µL of solution of tablets content, were spotted on TLC glass plats for separation of (Paracetamol, and Diclofenac Sodium) and quantification was carried out densitometerically at λ = 250 nm for Paracetamol,and λ = 290 nm for Diclofenac Sodium, and simultaneous quantification for two substances was carried out densitometerically at λ = 250 nm. The concentrations were calculated from the mentioned standard curves.

5. RESULTS AND DISCUSSION

5.1 Specific Surface Area of Acid Treated Bentonite (Acid Treated Syrian Clay): Specific Surface Area of treated bentonite was determined by the adsorption of Methylene Blue; it is found that the surface areawas 91 m^2/g.

5.2 Chromatograms processing: The position of the spots from the mobile phase front on the chromatographic plate for different concentrations (5 to 40 µg/spot) of Paracetamol, and (2 to 16 µg/spot) of Diclofenac Sodium at λ = 250 nm was **Fig. 3**.



a b

Figure 1. Chemical structure of a - Paracetamol , b – Diclofenac Sodium

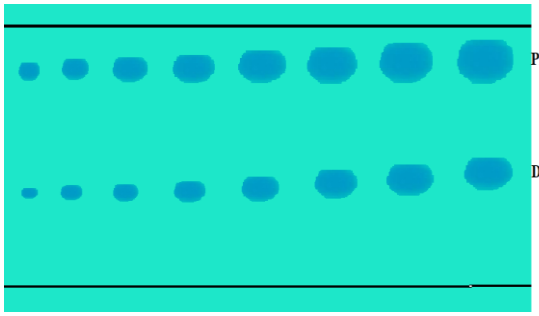


Fig. 3. TLC plate of standard mixtures of Paracetamol, and Diclofenac Sodium

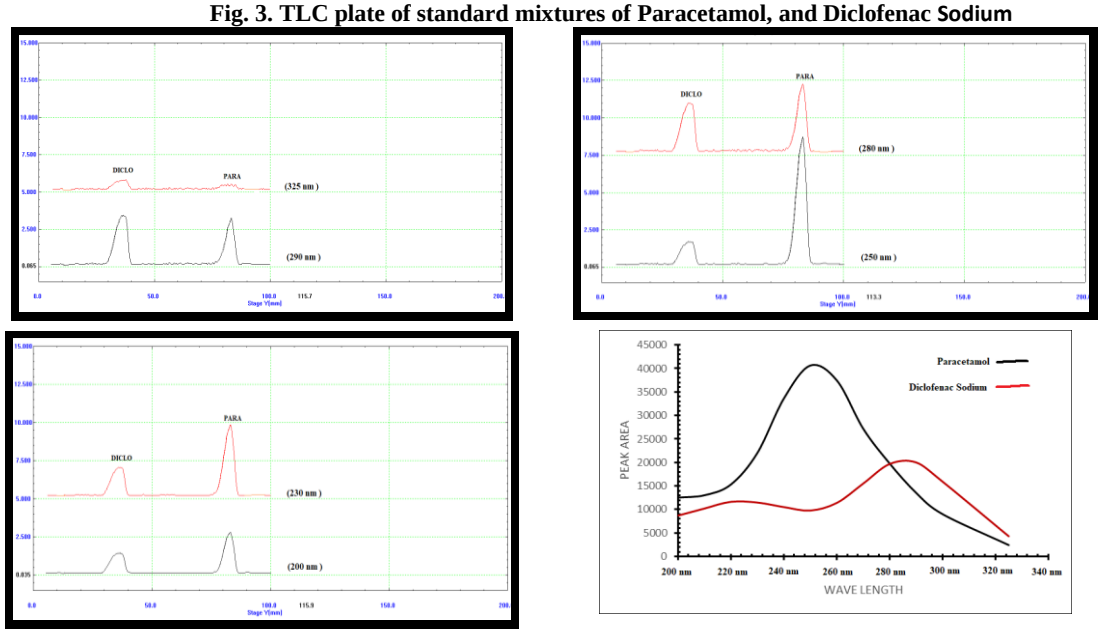


Fig.4 Chromatograms of mixture of Paracetamol, and Diclofenac Sodium at different wavelengths.

Fig. 5. Effect of wavelengths (λ) on peak areas of Paracetamol, and Diclofenac Sodium

TABEL 1: Analytical parameters of proposed method

Parameter	Paracetamol	Diclofenac Sodium
Linearity range, µg/spot	5- 40	2 - 16
Wavelength (nm)	250	290
Linear regression equation y=bx+c	Y=829.48X+8330.3	Y=693.12X+424.93
Correlation coefficient R^2	0.9959	0.9963
LOD (µg/spot)	0.0625	0.165
LOQ (µg/spot)	0.210	0.550
RSD%	2.00 % - 4.15%	2.48% - 4.97%

The chromatogram of mixture of Paracetamol, and Diclofenac Sodium (40 µg/spot for Paracetamol, and 16 µg/spot forDiclofenac Sodium) can be observed with two peaks at different wavelengths (λ) at 200 to 325 nm (Fig. 4). The first peak for Paracetamolincreases to λ = 250 nm then decreases, and the second for Diclofenac Sodiumincreases to λ = 290 nm then decreases (Fig. 4),&(Fig. 5) . It is inferred from the Figs. 4,and 5 that the best wavelengths to determination ofParacetamol, and Diclofenac Sodium were 250 nm, and 290 nm respectively. The retardation factors (R_f) of Paracetamol, and Diclofenac Sodium were 0.84 , and 0.35 respectively.

Quantitative evaluation: The method being validated through precision, linearity and accuracy for the simultaneous determination of different standard mixtures of Paracetamol, and Diclofenac Sodium in the range of 5.0 to 40.0 µg/spot for Paracetamol, and in the range of 2. 0 to 16.0 µg/spot for Diclofenac Sodium using λ = 250 nm , the results summarized in Table1.

Application: The results of the validation verify the suitability of the proposed analytical procedure for the identification and quantitative determination of Paracetamol, and Diclofenac Sodium in the mixture. Commercial product (that contained of the two studied Substance was analyzed in order to assign the values of their contents using λ = 250 for Paracetamol, and Diclofenac Sodium. The pharmaceutical formulation was selected for the study as the following:

Tablets: Each tablet of DICLOGESIC contains (500 mg Paracetamol , and 50 mg Diclofenac Sodium) , and each tablet of DICLOCIN contains (250 mg Paracetamol , and 50 mg Diclofenac Sodium).

The results are in good agreement with the results of HPLC. It can be observed that the difference between the results by HPLC and the found values by this method are less than 5 % in and the relative standard deviation is not exceeding ± 5 %. The proposed method has been successfully applied to determine Paracetamol, and Diclofenac Sodiumin pharmaceutical formulations.

CONCLUSION

In the preceding method, determination of Paracetamol, and Diclofenac Sodium in pure form and Tablets pharmaceutical formulations by TLCdensitometric method using acid treated Bentonite and mobile phase: Ethyl acetate: Methanol: Strong ammonia solution (55:5:3) (v/v) has been applied.

Quantification was carried out densitometerically at λ = 250 nm for Paracetamol,and
λ = 290 nm for Diclofenac Sodium, and simultaneous Quantification for two substances was carried out densitometerically at λ = 250 nm. The retardation factors (Rf) of Paracetamol, and Diclofenac Sodium were 0.84, and 0.35, respectively.

Calibration curves were obtained in the range of 5.0- 40.0 µg/spot for Paracetamol, and 2.0 - 16.0 µg/spot for Diclofenac Sodium (at λ = 250 nm) for simultaneous determination of two substances in standard solutions, and Tablets pharmaceutical formulations.

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