ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24JUL384

Synchronous Study of *Cefadroxil and Probenecid* using Spectrophotometric Method with Expository Agents

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Abstract:- For the synchronous verification of Cefadroxil and Probenecid in original form and in medicine dual dosages, two much sensitive and accurate spectrophotometric techniques have been derived. Using these techniques, a novel idea of area under the curve-AUC-is put forth for the synchronous calculated of two medicines. *DDQ-(2,3-Dichloro-5,6-Dicyano-1,4-Benzoquinone)* is used an expository reagent in Method A, and between 389nm to 691nm to *DDQ*, applied and verified. *p-CA-(p-Chloranilicacid: 2,5–Dichloro-3,6–dihydroxy-1,4–benzoquinone)* an expository reagent and the between 399nm and 701nm to p-CA are used and verified in Method B. Techniques created, used in calibration plots by two expository reagents respectively i.e., DDQ and p-CA. Optical, expository limits to the single and synchronous verification of Cefadroxil and Probenecid are shown in tables. The procedures are valued and contrast to HPLC, with standard deviation-SD, *t*-test and *F*-test.

Keywords *- Synchronous Verification, Spectrophotometer, Cefadroxil, Probenecid, DURICEF Tablet, DDQ, P-CA, Charge Transfer – Complex (CTC), Validation.*

I. INTRODUCTION

The current study is to use pi-Acceptors as expository agents to create two straightforward and smooth, sensitive spectrophotometric methods to the synchronous verification of Cefadroxil and Probenecid in medicinal dual dose and original mixture forms.

A. Cefadroxil

Cefadroxil (formerly trademarked as DURICEF) is a broad-spectrum antibiotic of the cephalosporin, effective muchin Gram-positive and Gram-negative bacterial diseases. Its IUPAC Name: *(6R,7R)-7-{[(2R)-2-amino-2-(4-hydroxyphenyl)acetyl]amino}-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid* [1].

The para-hydroxy derivative of cephalexin, cefadroxil is a Ist-generation cephalosporin antibacterial medication and used similarly to treat mild to moderate susceptible diseases, including urinary diseases, reproductive diseases, skin diseases.

➢ *Structure of Cefadroxil*

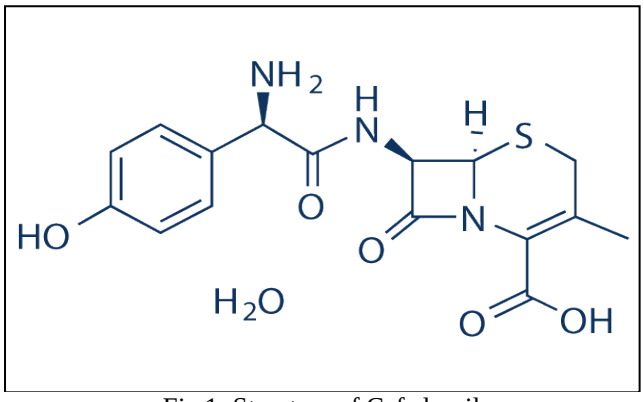

Fig 1: Structure of Cefadroxil

They are used to cure of diseases caused by Gram+ and Gram− type bacteria. These are act by inhibiting to prepare most essential components of bacterial cell boundary. They are safest and effective broad-spectrum anti-bactericidal antibiotics. [2,3] Only cephalosporin C is found naturally, and partially-synthetic cephalosporins are procured from 7-amino-cephalosporanic acid by the process of hydrolysis. [4] Among all publications verification of cephalosporins, Gas chromatography – GC, high performance liquid chromatography (HPLC), thin layer chromatography (TLC) and microbiological trials available widely. [4,5-12] Review explained HPLC conditions to synchronous purification of more than two cephalosporins. [13] An easy removing method was needed to verify contamination another one cephalosporin. The easy, fast assay method for the verified of cefadroxil in bulk form is developed. The process gives separation, linear and hygienic different range of strength.

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B. Probenecid

It is initially used in treating gout and hyperuricemia and its IUPAC Name is 4-(dipropylsulfamoyl) benzoic acid. Probenecid; (4-(Dipropylsulfamoyl) benzoic acid) [14] is a uricosuric agent used to the cure of hyperureciemia along with chronic, hyperuricemia caused by diuretic therapy and as adjunct to some antibacterial to lose their renal tubular excretion [15]. Probenecid was prepared as an alternative to caronamide [16].

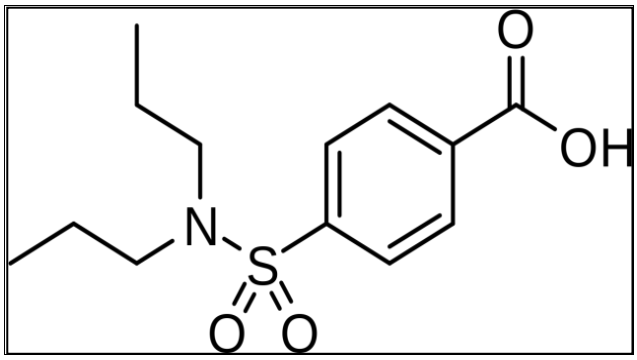

Fig 2: Probenecid

➢ *Structure of Probenecid*

Decreasing serum urate levels in the body [17]. The literature review revealed that numerous procedureshave been applied for the analysis of probenecid in a single dosage form HPLC [18-21], TLC [22-23], Also, different methods reported for the single verified of colchicine as HPLC, and spectrophotometry. This is thought to develop easy and fast procedures which can be applied in quality control laboratories – QC for the verified of both drugs synchronously. spectrophotometric [24- 27], capillary electrophoresis [28].

Recently, our laboratory has published reports on the simultaneous spectrophotometric measurement of Levofloxacin and Azithrmycin, Azithromycin and Ofloxacin in their dual dose form [29, 30]. Simultaneous determination of lamivudine and zidovudine using πacceptors as analytical reagents: a spectrophotometric study [31]. Evulsions spectrophotometric determination of cycloserine in pharmaceutical formulations with BPB and BCG dyes [32].

Medicine dual dose and in original new novel methods are proposed in this study for the synchronous verification of probenecid and cefadroxil.

II. MATERIALS AND METHODS

A. Instruments

The study's UV-Visible spectra were encountered by *quartz cells* with a 10mm path length on the SHIMADZU 140 double beam spectrophotometer and the ELICO SL - 210 UV-Visible double beam spectrophotometer. To read pH, an Elico model Li-120 pH meter was used.

B. Materials

DDQ (2,3-Dichloro-5,6-dicyano-p-benzoquinone) obtained from Fine Chemicals-SD, Mumbai. It was twice solidified as in ration of 3:1 chloroform:benzene combination. The Rolex, Mumbai-supplied p-CA (p-chloranilic acid) was utilized without additional purification. Throughout the process, acetonitrile of HPLC grade was employed. Hetero Drugs Private Ltd. in Hyderabad and Dr. Reddy's laboratory provided the medications Cefadroxil, Probenecid, and the drug cocktail that was analyzed.

C. Methods and Calibration

➢ *Method 1 – DDQ*

Using *DDQ-(2,3-Dichloro-5,6-dicyano-1,4-benzoquinone)* as an expository reagent, this approach developed to synchronous verification of Cefadroxil and Probenecid in original form and in medicine dual dosages. A sequence of 10mL flasks were filled with varying aliquots (1–9mL) of Cefadroxil, 1mL of *DDQ*, and solvent (acetonitrile) to make up the remaining volume. After giving the chemicals a good shake, UV-Visible spectra were recorded. The *DDQ* anion's optical density-OD at 480, 540, and 580 nm was recorded. From the spectra, the areas under the curve-(AUC) for *DDQ* between 389and 691nm were calculated. Plotting AUCx against Cefadroxil concentration was done. Similarly ccomparable trials were also conducted again to verification of K_y for Probenecid.

The same ratio used in the medicine formulations was used to generate the stock of the Cefadroxil and Probenecid mixture. 1mL of *DDQ* reagent was introduced to a sequence of standard flasks containing 1–9 mL of the drug solution from the stock. Acetonitrile, the solvent, was used to make up the remaining volume. The chemical solutions were thoroughly shaken. The UV-Visible spectrum was encountered.

The OD at 480, 540 & 580 for DDQ anion were noted. AUC_{mix} was plotted against either Cx or Cy for calibration.

➢ *Method2-p-CA*

This technique uses p-CA-(p-Chloranilic acid: 2,5-Dichloro-3,6-dihydroxy-1,4-benzoquinone) as an expository reagent to calculate medicine synchronously in a dual combination. A sequence of 10mL flasks filled with different aliquots (1–9mL) of Cefadroxil, 1mL of p–CA, and solvent (acetonitrile) to prepare up the remaining volume. After giving the chemical solutions a good shake, UV-Visible spectra recorded. The p-CA anion's OD at 540nm was recorded. The spectra were used to calculate the areas under the curve (AUC) for p-CA between 399 and 701nm. Plotting AUCx against medication concentration is done. Kx was calculated from the plot's slope. Analogous tests were also conducted again to determine Ky for Probenecid.

The same ratio in the medicine formulations was used to generate the stock of the Cefadroxil and Probenecid mixture. 1–9mL of the medicine ratio were taken from the stock and put to a sequence of standard flasks along with 1mL of the p–CA reagent. Acetonitrile, as the solvent used to make up the

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24JUL384

remaining volume. The chemical solutions were thoroughly shaken. Record of UV-visible spectra were made. The p-CA anion's optical density-ODs at 540nm were recorded. For plots of calibration, AUCmix also plotted verses either Cy or Cx.

III. RESULTS AND DISCUSSION

The Charge Transfer complexes-(CTC) are produced by the molecular collisions between electron donors and acceptors. These electron donor and acceptor collisions are recorded spectrophotometrically to the calculate drugs since these collisions are generally along to the generation of intensely colored CTCs, which absorb radiation in the visible area. The absorption bands of these complexes should be used for the quantification of electron donor drug molecules (Scheme).

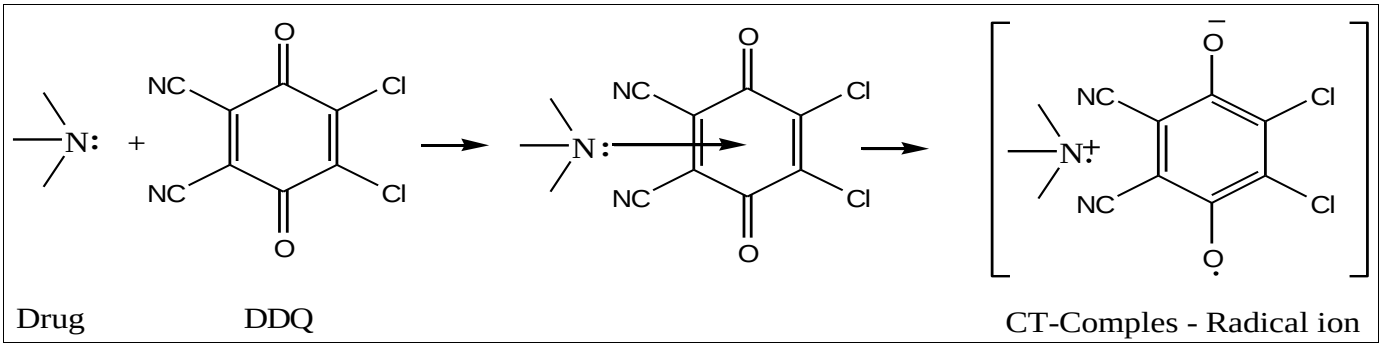

Image 1: CT-Comples - Radicalion

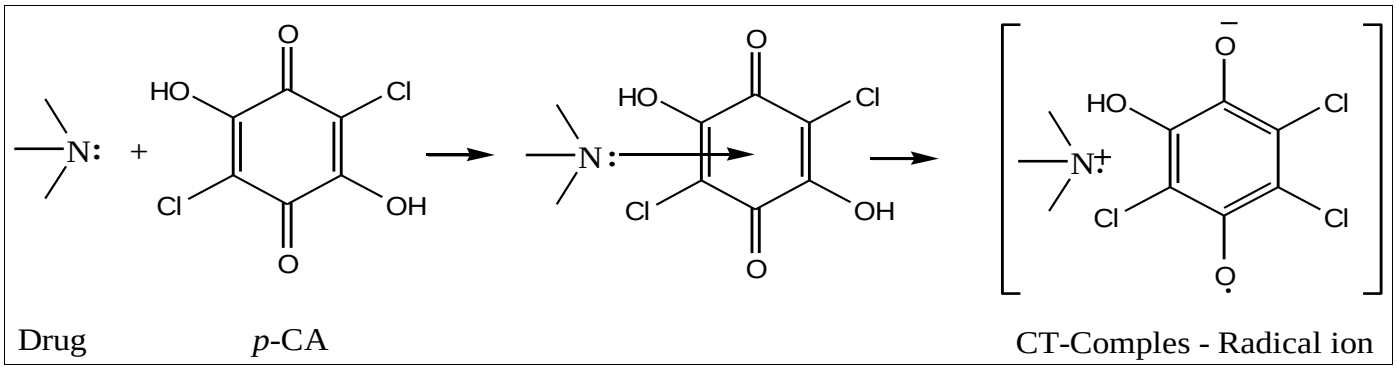

Image 2: SCHEME - The Structures of Pi-Acceptors and CT-Complex between Drug and Pi-Acceptors

For instance, the expository reagent p-CA is independent of the medication and yields a band for the p-CA anion at 540nm. It also displays a band at 540nm and is anticipated to colloid with both medications in a dual cocktail. Even though the expository wavelength is the same, it is still possible to examine each component's concentration because of the variations in the quantity of interaction in the combination. The author was inspired to write these lines after considering this. Typically, optical density-OD at λmax is evaluated in relation to drug concentration for calibration purposes in order to do quantification. The area under the curve-(AUC), according to the authors, is a better measure than optical density.

AUC (Area under curve in mixture) = $AUC_X + AUC_Y$

Where,

X and Y are two drugs in the dual mixture

But

AUC of X α C_X

And
AUC of Y α C_Y
$AUC_X = K_X C_X$
$AUC_Y = K_Y C_Y$
$AUC_{mix} = K_X C_X + K_Y C_Y$ …….. (1)

Dividing both sides of equation by $K_X C_X$

$$\frac{AUC_{mix}}{K_x C_x} = 1 + \frac{K_Y C_Y}{K_x C_x}$$

$$\text{But} \quad \frac{K_Y C_Y}{K_x C_x} = K \text{ (Constant)}$$

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$$\frac{AUC_{mix}}{K_xC_x} = 1+ K$$

$AUC_{mix} = (1 + K) K_XC_X$

$AUC_{mix} = (K_X + K, K_X) C_X$ ……..… (2)

Similarly,

$AUC_{mix} = K_XC_X + K_YC_Y$

Dividing both sides with K_YC_Y

$$\frac{AUC_{mix}}{K_YC_Y} = 1+ \frac{K_xC_x}{K_YC_Y}$$

$$\frac{K_xC_x}{K_YC_Y} = K \text{ (Constant)}$$

$AUC_{mix} = (1 + K) K_YC_Y$ ……..… (3)

$AUC_{mix} = (K_Y + K. K_Y) C_Y$ ……..… (4)

The equations 2 and 4 imply that AUCmix is either proportional to Cx or C_Y. Possible to new calibration plots to identify the one drug concentrations in dual forms by calculating AUCmix to a forms of medications with a constant ratio. A sequence of 10mL flasks filled with various aliquots (1–9mL) of the medication Cefadroxil, 1mL of DDQ or p-CA, and the remaining volume filled with acetonitrile as solvent. After giving the chemical solutions a good shake UV-Visible spectra recoreded. The ODs for the p-CA anion at 540 nm and the DDQ anion at 480,540, and 580nm were recorded. The spectra used to calculate the area under the curve-(AUC) between 399 and 701nm for p-CA and between 389 and 641nm for DDQ (Image 3 and 4).

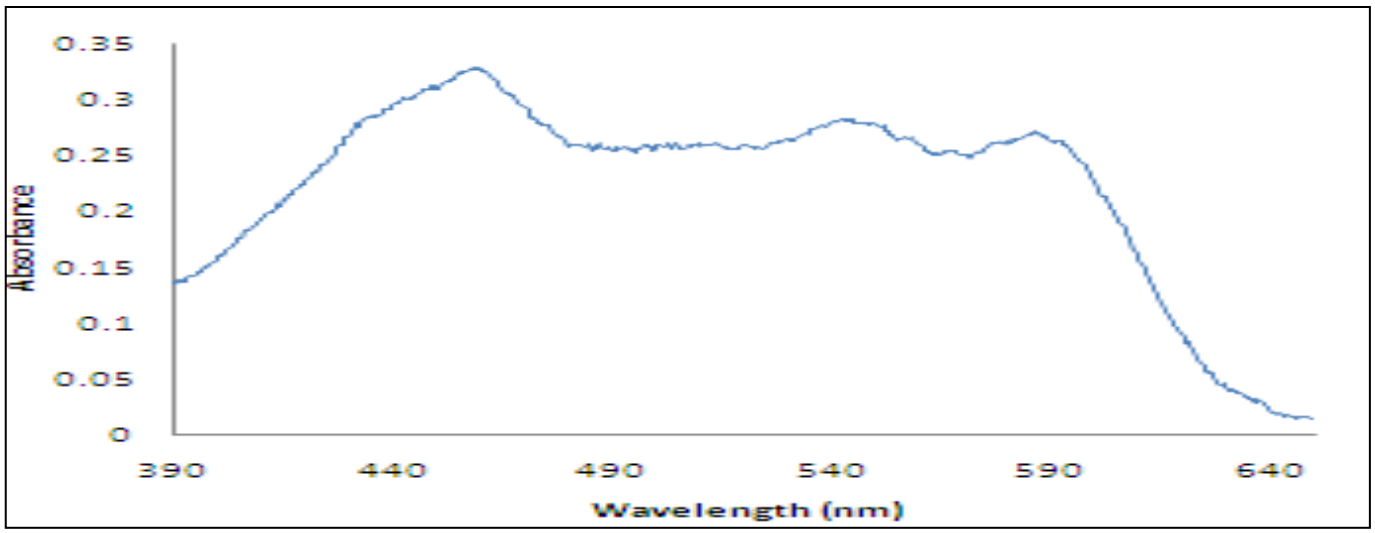

Image 3: Cefadroxil with DDQ – CT-Complex

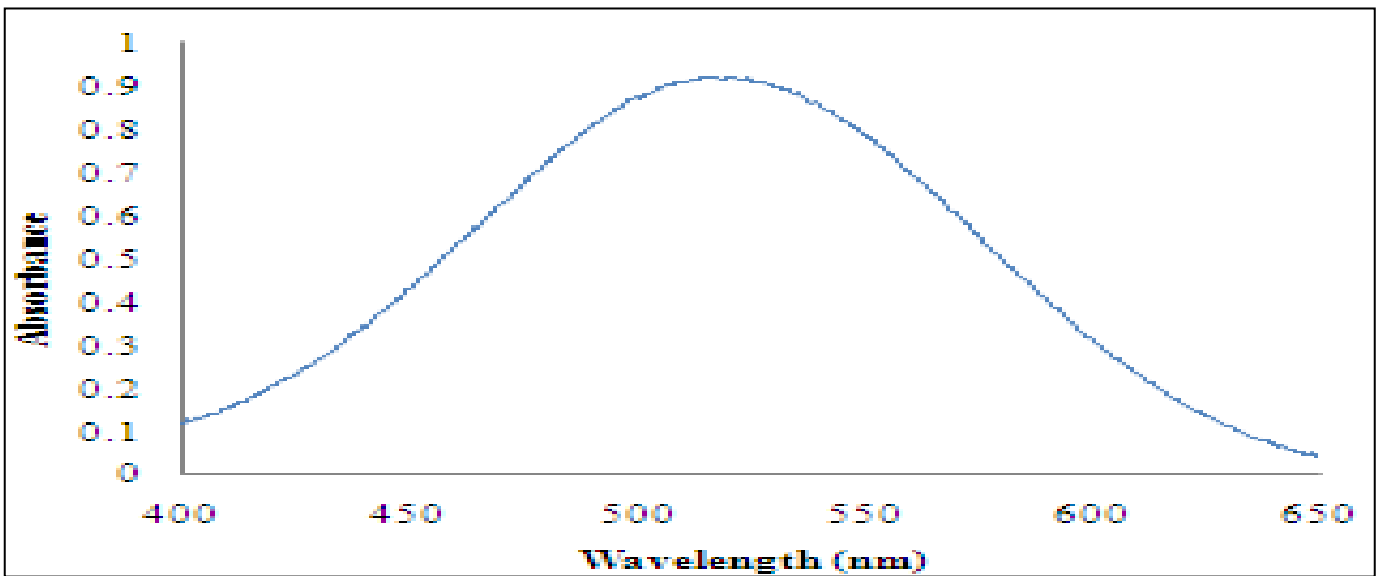

Image 4: Cefadroxil with *p*-CA-CT-Complex

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➢ *The Plots of AUC_x vs Concentration of Probenecid with DDQ and p-CA are Shown in Images 5 and 6.*

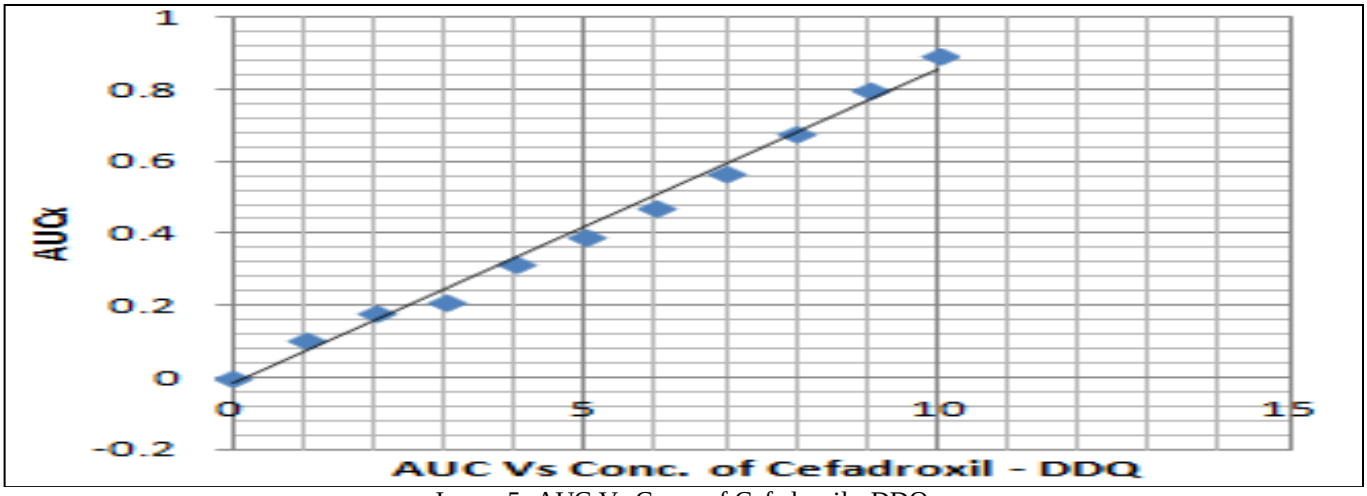

Image 5: AUC Vs Conc. of Cefadroxil - DDQ

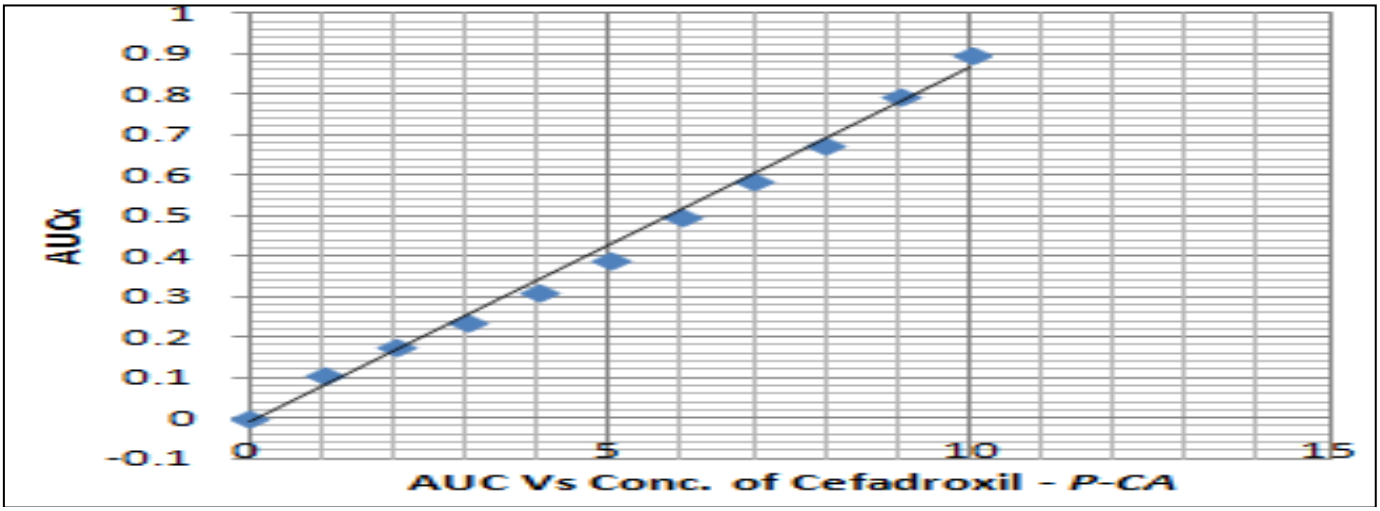

Image 6: AUC Vs Conc. of Cefadroxil – *P-CA*

From the slope K_x was verified. In the Same Way, Analogous Experiments Repeated and Verified of K_y to Probenecid (Images 7, 8, 9 and 10).

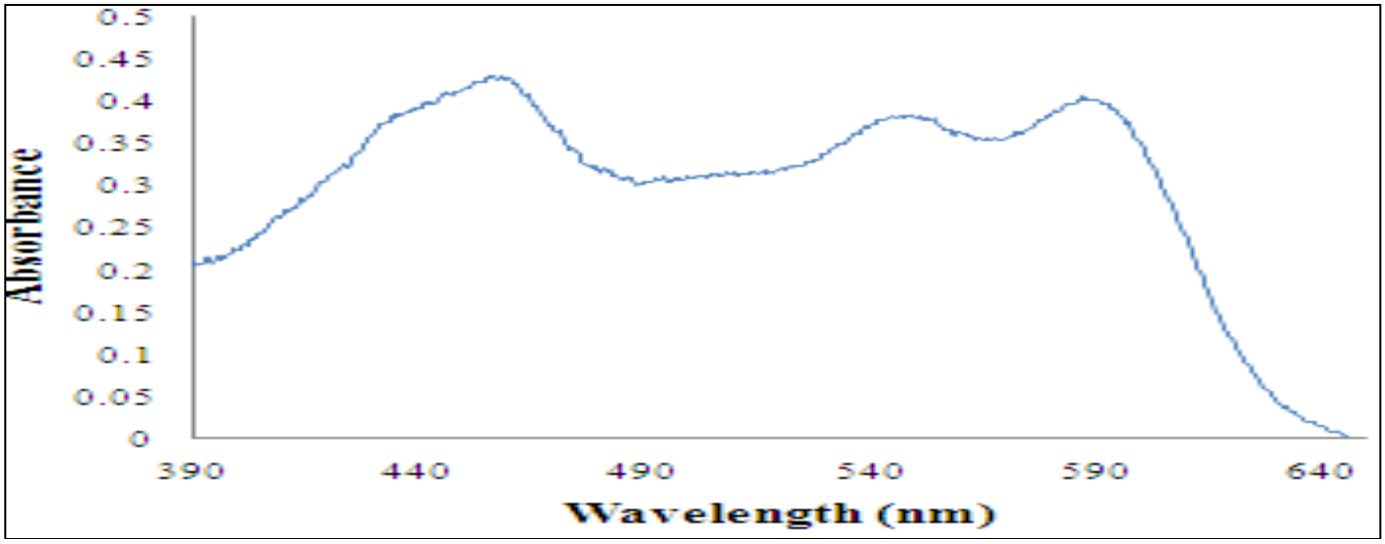

Image 7: Probenecid with DDQ-CT-Spectrum

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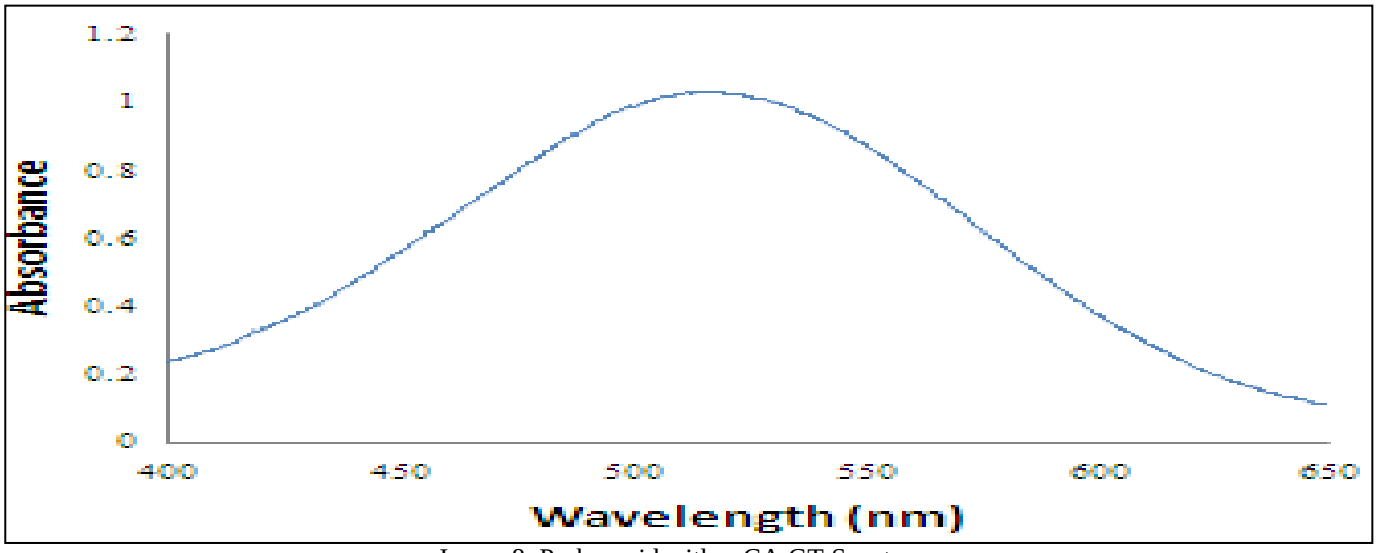

Image 8: Probenecid with p-CA-CT-Spectrum

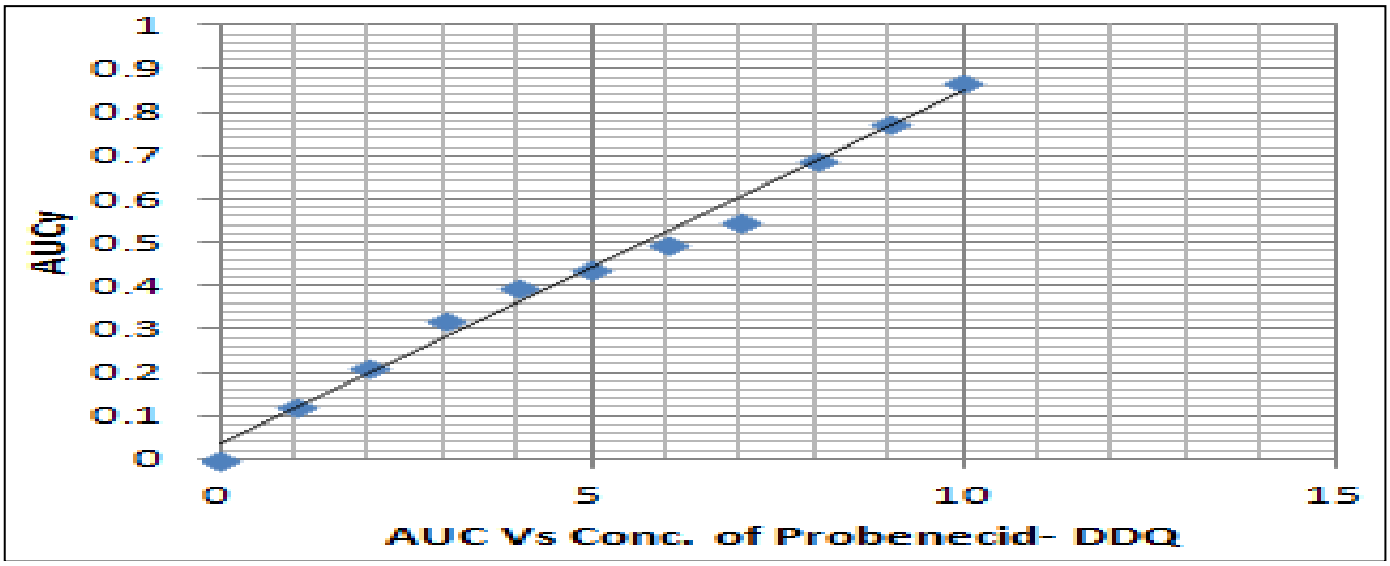

Image 9: AUC Vs Conc. of Probenecid - DDQ

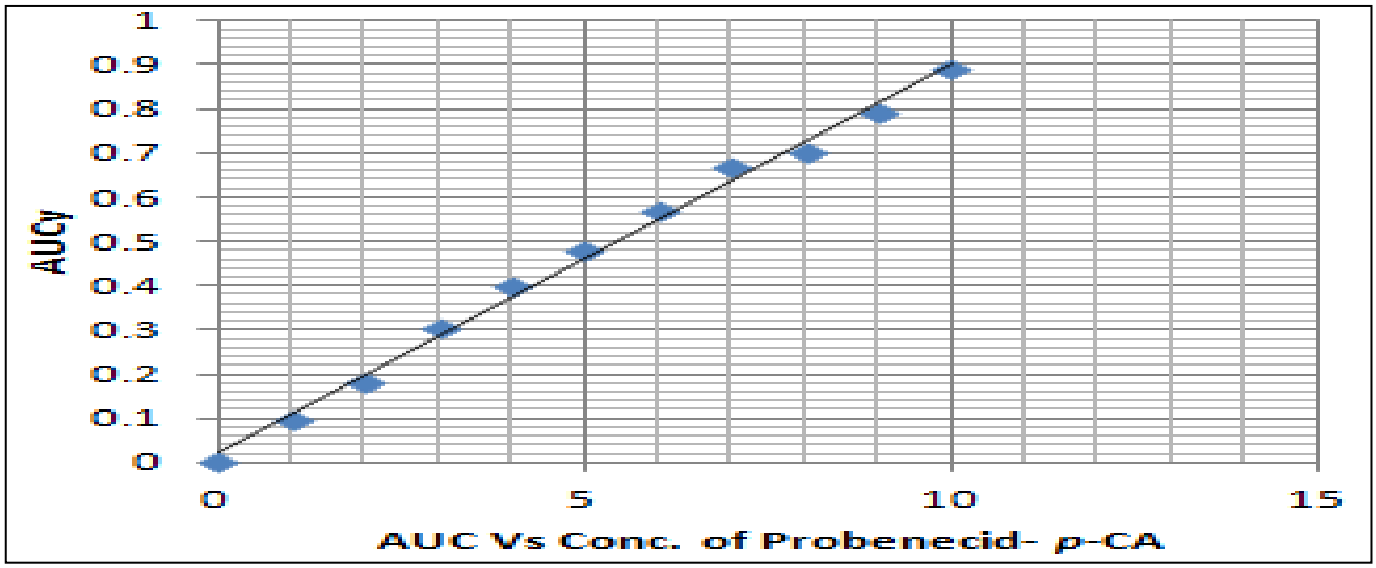

Image 10: AUC Vs Conc. of Probenecid – *p*-CA

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24JUL384

Cefadroxil and Probenecid were mixed in the same ratios as the medicine tablet formulations to create a stock. 1mL of substance DDQ or p-CA was poured in sequence standard flasks containing 1to9mL of a drug mixture procured from the stock. Acetonitrile used to make up the remaining volume. The chemical solutions were thoroughly shaken and recorded UV-visible spectra (Images11and12). Procured from the spectra (Images3and4).

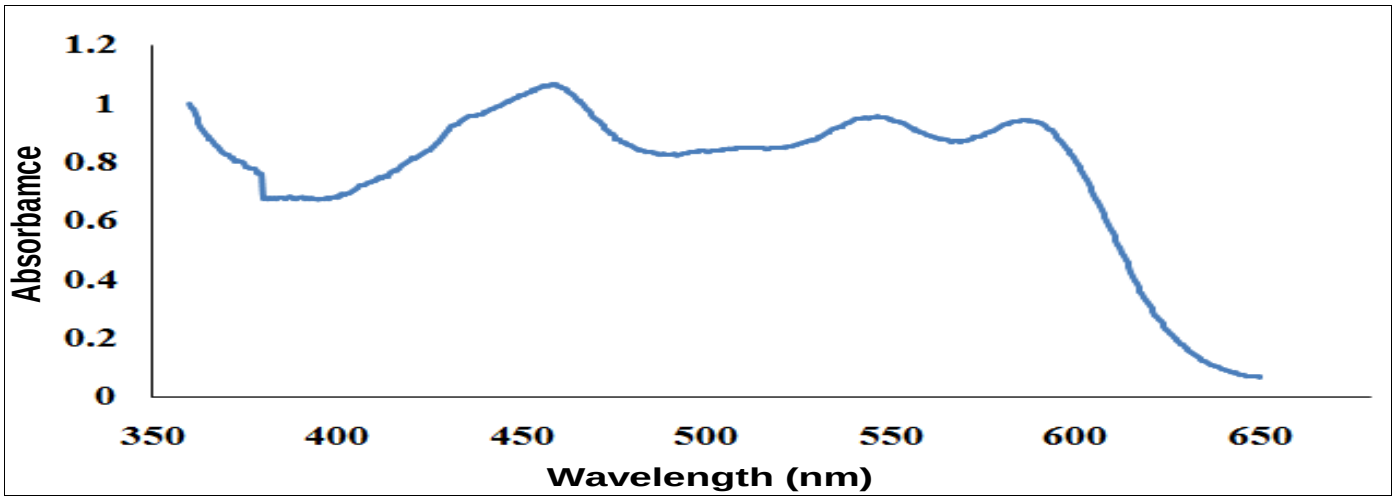

Image 11: Cefadroxil and Probenecid with DDQ in original form in CT-Spectrum

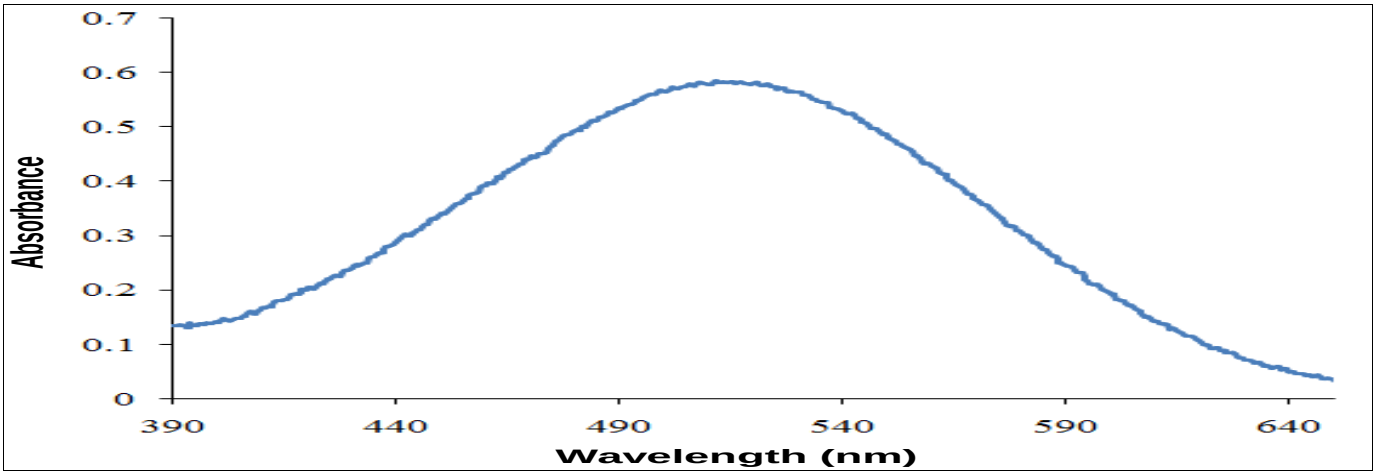

Image 12: Cefadroxil and Probenecid with p-CA in Original form in CT-Spectrum

The p-CA anion's OD at 540nm and the DDQ anion's at 480, 540, and 580nm were recorded. Plots of AUCmix were made using either Cy or Cx (Images13 and 14).

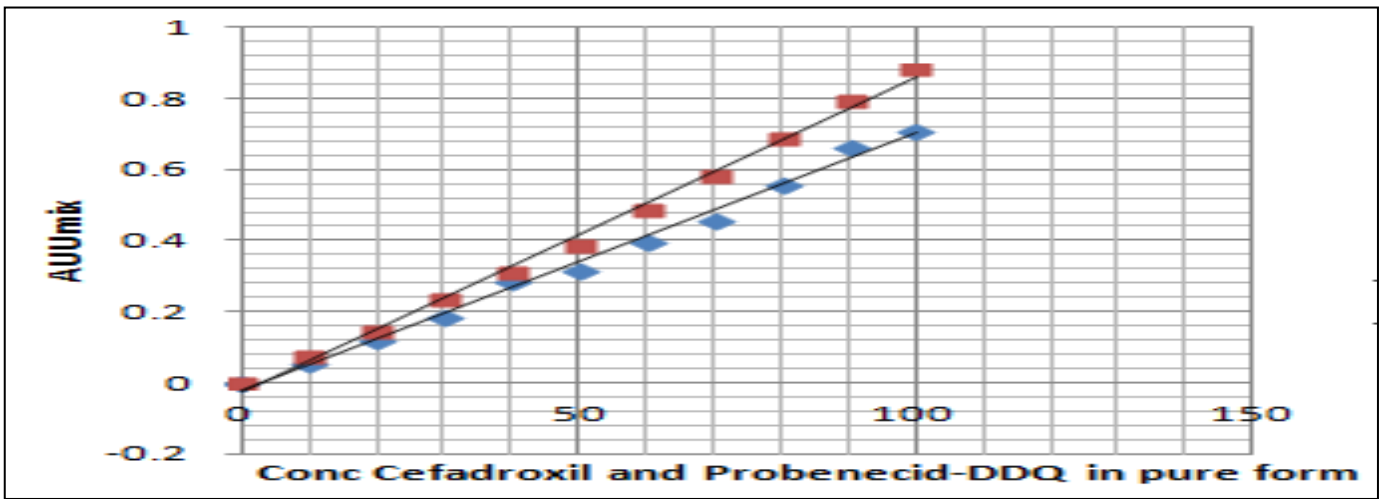

Image 13: Conc Cefadroxil and Probenecid-DDQ in Pure Form

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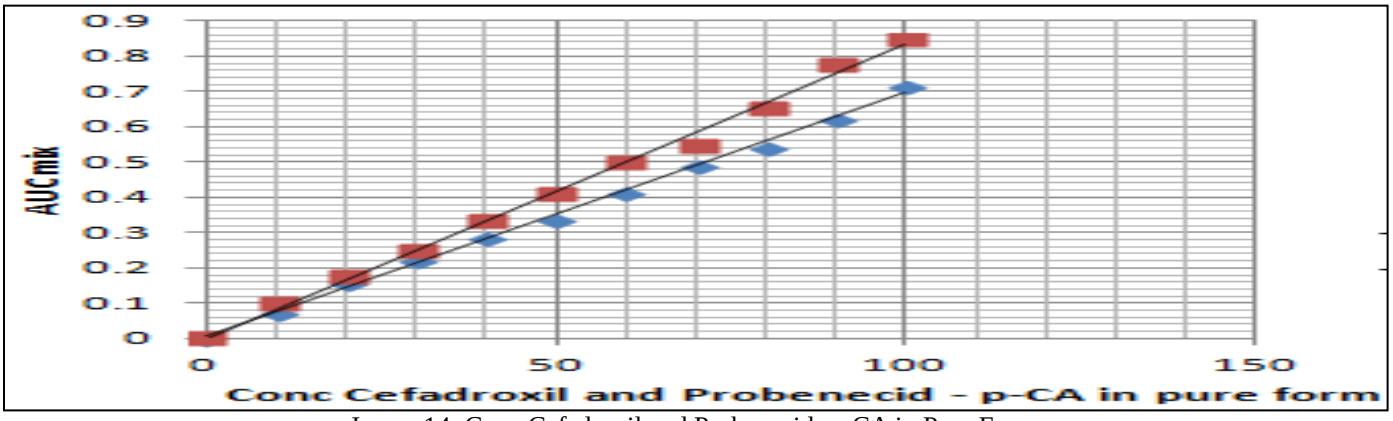

Image 14: Conc Cefadroxil and Probenecid- p-CA in Pure Form

Table1 presents the optical, statistical properties information for the equation of regression to the suggested method for the verified of one drug of Cefadroxil and Probenecid, and Table2 presents the prepared ratio of drugs in the 1:1 ratio (Cefadroxil and Probenecid) as medicines using area under curve(AUC).

Table 1: The individual Optical and Expository Limits of Cefadroxil and Probenecid by AUC

Limits	**DDQ**		**p-CA**	
λLeast and λbig AUC	389-651		399-701	
Sequence (μgmL^{-1})	**Cefadroxil**	**Probenecid**	**Cefadroxil**	**Probenecid**
	5-60	5-60	25-300	25-300
Slope	3.456	1.202	0.228	0.094
Intercept	-0.310	0.333	0.256	0.286
Correlation coefficient	0.997	0.999	0.999	0.989
Residual intercept	0.3190	0.3762	0.1551	0.5190
LOD	0.8	1.4	1.6	1.5
LOQ	2.32	3.32	6.25	5.85

Table 2: The Synchronously Calculation of Optical and Expository Limits of Cefadroxil and Probenecid in Synthetic Mixture in the Equal Ratio by AUC

Limits	**DDQ**		**p-CA**	
λLeast and λbig AUC	389-651		399-701	
Sequence (μgmL^{-1})	**Cefadroxil**	**Probenecid**	**Cefadroxil**	**Probenecid**
	5-100	5-100	25-500	25-500
Slope	1.91	5.78	2.13	1.341
Intercept	0.422	2.446	-2.069	1.115
Correlation coefficient	0.984	0.997	0.999	0.999
Residual intercept	0.316	0.912	1.525	0.583
LOD	0.5	0.5	2.5	2.5
LOQ	1.65	1.65	8.25	8.25

After choosing five distinct original drug mixture solutions within the calibration curve's range, recovery studies were carried out. Table3 tabulates the recoveries mix with its suitable standard deviation-SDs.

Table 3: The Synchronously Calculation of Optical and Expository Limits to Cefadroxil and Probenecid in Synthetic Mixture in the Equal Ratio by AUC as Application

Take ($\mu g\ mL^{-1}$)				**Found ($\mu g\ mL^{-1}$)**				**Recovery (%)**			
Cefadroxil		**Probenecid**		**Cefadroxil**		**Probenecid**		**Cefadroxil**		**Probenecid**	
DDQ	**p-CA**	**DDQ**	**p-CA**	**DDQ**	**p-CA**	**DDQ**	**p-CA**	**DDQ**	**p-CA**	**DDQ**	**p-CA**
5	5	10	10	4.81	4.95	10.12	10.24	96.2	99	101.2	102.4
10	10	20	20	10.35	10.26	20.06	20.63	103.50	102.61	100.3	103.13
15	15	30	30	15.15	15.14	30.19	30.12	101.01	100.92	100.63	100.4
20	20	40	40	19.95	19.83	40.86	40.82	99.75	99.15	102.15	102.05
25	25	50	50	25.14	25.04	50.04	50.06	100.56	100.16	100.08	100.12
30	30	60	60	30.08	29.94	59.91	59.15	100.26	99.8	99.85	98.58

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24JUL384

t-Test				F-test			
Cefadroxil		Probenecid		Cefadroxil		Probenecid	
DDQ	p-CA	DDQ	p-CA	DDQ	p-CA	DDQ	p-CA
0.0128	0.0126	0.2346	0.0781	1.0830	0.7564	0.8751	1.0462

SD Developed				SD Reference			
Cefadroxil		Probenecid		Cefadroxil		Probenecid	
DDQ	p-CA	DDQ	p-CA	DDQ	p-CA	DDQ	p-CA
1.3546	1.1580	0.5643	0.2845	1.6485	1.1532	0.3842	0.2006

Similarly, different solutions of **DURICEF** tablets (Cefadroxil:Probenecid) trials was verified using the calibration plot and calibration plot sequences (Image 15 and 16). Table 4 tabulates the recovery calculations of experiments in results data.

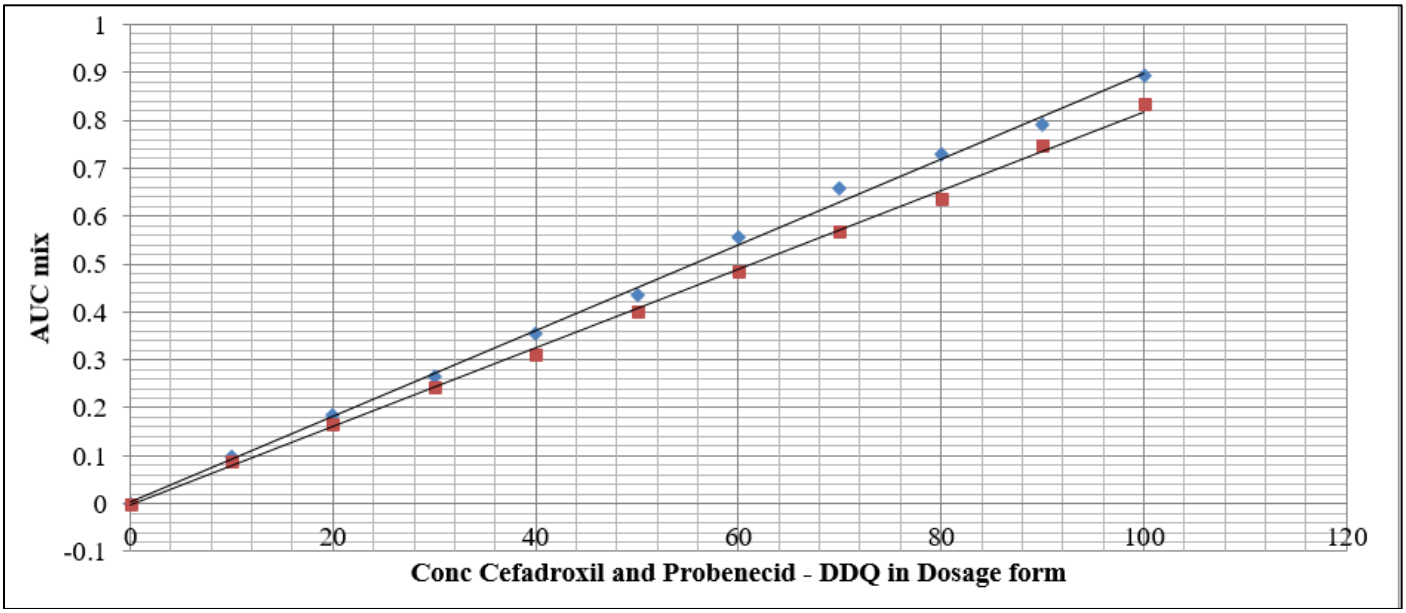

Image 15: Conc Cefadroxil and Probenecid - DDQ in Dosage form

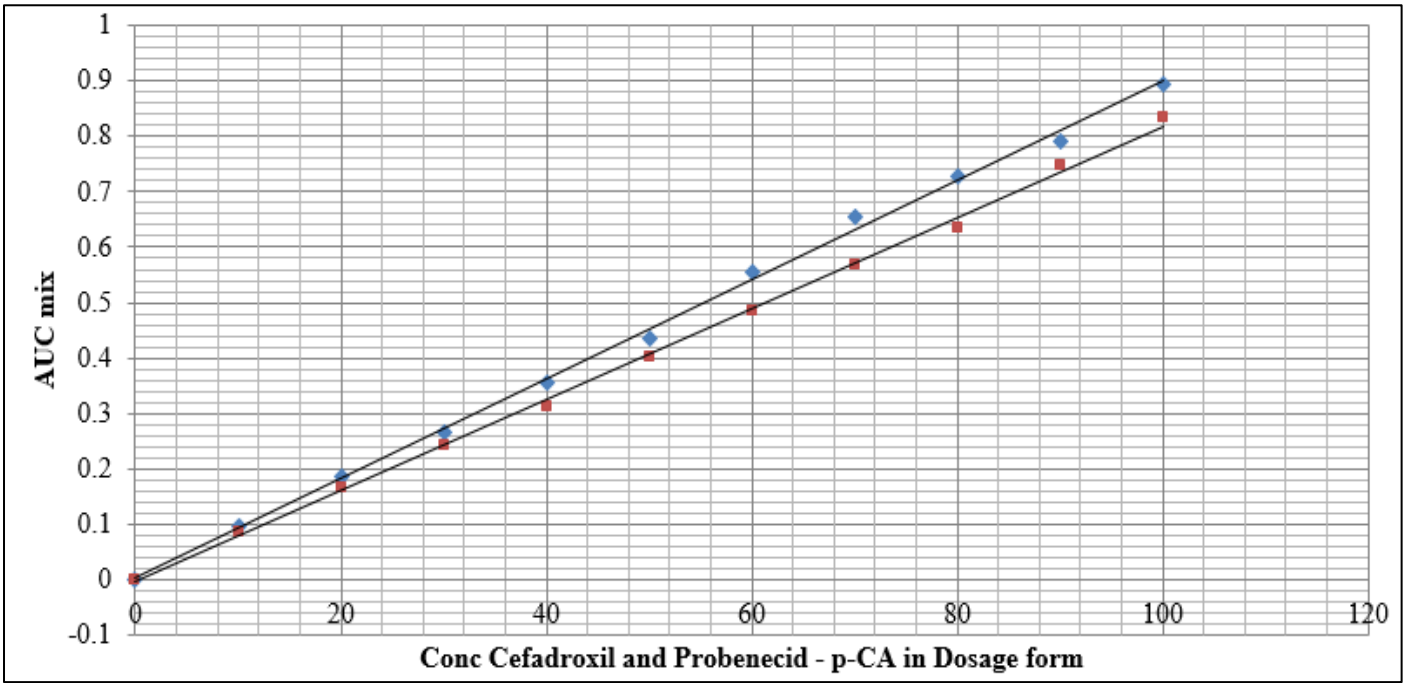

Image 16: Conc Cefadroxil and Probenecid - *p*-CA in Dosage form

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24JUL384

Table 4: The Synchronous Calculation of Cefadroxil and Probenecid in the Equal Ratio of Drugs in Medicine form DURICEF as Application Using AUC.

Taken ($\mu g\ mL^{-1}$)				**Found ($\mu g\ mL^{-1}$)**				**Recovery (%)**			
Cefadroxil		**Probenecid**		**Cefadroxil**		**Probenecid**		**Cefadroxil**		**Probenecid**	
DDQ	**p-CA**	**DDQ**	**p-CA**	**DDQ**	**p-CA**	**DDQ**	**p-CA**	**DDQ**	**p-CA**	**DDQ**	**p-CA**
5	5	10	10	4.8	4.69	10.03	10.04	96.00	93.88	100.3	100.4
10	10	20	20	9.6	9.72	20.05	20.85	96	97.2	100.25	104.25
15	15	30	30	14.5	15.06	30.01	30.26	96.66	100.16	100.03	100.86
20	20	40	40	19.86	20.24	39.56	40.24	99.3	101.2	98.9	.100.6
25	25	50	50	23.43	24.82	48.12	49.64	93.72	99.28	96.24	99.28
30	30	60	60	29.26	30.05	59.26	59.06	97.53	100.16	98.76	98.43

SD Developed				**SD Reference**			
Cefadroxil		**Probenecid**		**Cefadroxil**		**Probenecid**	
DDQ	p-CA	DDQ	p-CA	DDQ	p-CA	DDQ	p-CA
1.3763	0.3583	1.1337	0.8468	1.3132	0.3454	0.9156	0.7607

t-Test				**F-test**			
Cefadroxil		**Probenecid**		**Cefadroxil**		**Probenecid**	
DDQ	p-CA	DDQ	p-CA	DDQ	p-CA	DDQ	p-CA
0.1818	0.1115	0.2105	0.2018	0.8445	1.1761	0.7455	0.7852

IV. CONCLUSION

Using π-acceptors, DDQ and p-CA, two new sensitive and accurate techniques are suggested for the synchronous verification of Cefadroxil and Probenecid in dual mixture. The idea of area under curve (AUC) serves as the foundation for these techniques. These methods are tested and validated as per guidelines of the ICH and can be applied for the synchronously calculation of Cefadroxil and Probenecid in a dual mixture in medicines in R&D laboratories.

ACKNOWLEDGEMENTS

The authors are thankful for helpful discussions and to Dr. T. Veeraiah Principal (Retd.,) SAP College, Vikarabad for providing lab facilities and Dr. M. Janga Reddy, Director, CMRIT-Hyderabad, Kandlakoya, Medchal Malkajagiri, for the help of R & D cell.

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