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Research Article

# DISSOLUTION PROFILING OF BILAYERED CONVENTIONAL RELEASE PARACETAMOL AND SUSTAINED RELEASE DICLOFENAC SODIUM (BY SIMULTANEOUS ESTIMATION METHOD UV)

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**ABSTRACT**

The prescription for inflammatory joint diseases, degenerative disease, lumbago, sciatica, neuralgia, myalgia, migraine attacks and 70 % of over counter drugs falls for paracetamol and diclofenac sodium. So the objective of the study is to have a dissolution profile of bilayer tablet with reference to marketed product crocin® and voveran® by simultaneous estimation of paracetamol and diclofenac from the dissolution media. The design of experiment for paracetamol was done by trilinear graph considering the main factors as crospovidone, mircocrystalline cellouse and starch. Hydroxypropyl methylcellulose was used as a martixing agent for diclofenac sodium. The invitro drug behavior of diclofenac sustained release was compared with marketed product and they are fitted to Hicughi model. The bilayered tablet was manufactured by taking the optimized batch and the dissolution profiles were compared.

**Keywords:** Bilayer tablets, Paracetamol, Diclofenac sodium, Dissolution profiling, Trilinear graph, Simultaneous estimation.

## INTRODUCTION

Diclofenac sodium a NSAID (non-steroidal anti-inflammatory drug) which belongs to amino phenyl acetate and it's of synthetic origin. It belongs to cyclo-oxygenase inhibitor by mechanism of action and also classified as analgesics and anti-inflammatory agents pharmacologically. Its used in inflammatory joint diseases, degenerative disease, lumbago, sciatica, neuralgia, myalgia, extra articular tissue disease, post traumatic pain syndromes, which are accompanied by inflammation, postoperative pain, acute gout, primary disalgomenoreya, adnexitis, migraine attacks, renal and hepatic colic, infections of upper respiratory tract, residual effects of pneumonia[1,2].

Paracetamol an N-(4-hydroxyphenyl) ethanamide used as analgesic and antipyretic agent. Paracetamol active metabolite of phenacetin, responsible for its analgesic effect [3, 4]. Paracetamol a weak prostaglandin inhibitor in peripheral tissues and possesses no significant ant inflammatory effects. Its one of the most important drugs used for the treatment of mild to moderate pain when an anti inflammatory effect is not necessary. Paracetamol preferred over aspirin as an analgesic antipyretic for patients in whom aspirin is contraindicated, such as those who have a history of gastric ulcer or a coagulation disorder [5, 6].

The literature survey revealed that there is no simultaneous estimation for dissolution profile of conventional release paracetamol and sustain release diclofenac sodium. This present work describes an absorption ratio method for simultaneous determination of these drugs.

## MATERIALS AND METHODS

Paracetamol, diclofenac sodium, microcrystalline cellulose (Avicel PH 102), were received as gift samples from Rechem Hyderabad. Starch, lactose, crospovidone (XL) and hydroxypropylmethylcellulose (HPMC K4M), Magnesium stearate, talc was purchased from SD fine chemicals. Voveran® SR and Crocin® 500 were purchased from local pharmacy.

The design of experiment was made with software Design expert® (full version) using trilinear graph considering the factor of concentration of excipients used[7]. The excipients considered are microcrystalline cellulose (filler), starch (binder), crospovidone XL (superdisintegrant)[8,9]. The corner points (figure.1) are not taken for experimental trials as the one component only cannot be used for formulation. PF1, PF2, PF3, PF4 points experiments are done and the granules obtained from that experimental points were used to make tablets which had been compared against crocin® marketed product.

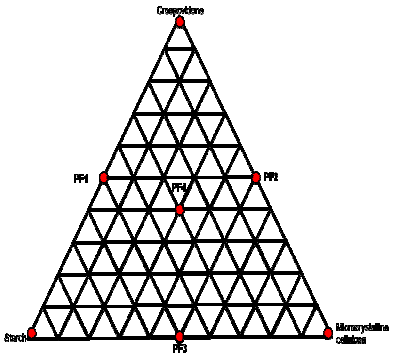


**Fig. 1: Design of experiment for paracetamol**

### Preparation of paracetamol tablets

Paracetamol, microcrystalline cellulose, and fraction of crospovidone were granulated by starch solution which was prepared by adding 60°C water. Then the wet mass was passed through 20# sieve to obtain granules then the granules are dried at 75°C. Then the granules obtained are blended with crospovidone, talc, magnesium stearate[10]. The tablets are made from each group of formulation then they are evaluated for weight variation, friability, hardness, disintegrating time and dissolution. In dissolution the screening criteria taken into consideration was t60 value (time taken to dissolute 60% of the drug in solution)[11].

### Evaluation of paracetamol tablets

The tablets were compressed by rotary tablet press (Karanavathi & Co.) with caplet shaped die and punch of size19.2mm. Invitro comparison was performed for formulated tablets and marketed Crocin®. Formulation PF3 shows better relevance results on comparison from table1.

### Preparation of diclofenac tablets

Diclofenac sodium, lactose was mixed and granulated with HPMC solution made by a blend of dichloromethane and isopropyl alcohol in 1:1 ratio. Then the wet mass was passed through 20# sieve to obtain granules then the granules are dried at 45°C. Then the granules obtained were blended with talc, magnesium stearate. The tablets were evaluated for weight variation, friability, hardness and dissolution[12].

**Evaluation of diclofenac sodium tablets**

The tablets prepared by rotary tablet press (Karanavathi & Co.) with caplet shaped die and punch of size19.2mm. The prepared tablets were compared invitro with marketed tablets of Voveran®, the dissolution profile was fitted to higughi model[13] and formulation DF4 shows better relevance results on comparison from table 4.

**Table 1: Formulation of paracetamol granules**

| Ingredients | PF1 (mg) | PF2 (mg) | PF3 (mg) | PF4 (mg) |
|---|---|---|---|---|
| Paracetamol | 500 | 500 | 500 | 500 |
| Starch | 50 | - | 50 | 66 |
| Microcrystalline cellulose | - | 75 | 75 | 80 |
| Crospovidone | 3 | 3 | - | 3 |
| Talc | 1 | 1 | 1 | 1 |
| Magnesium stearate | 1 | 1 | 1 | 1 |

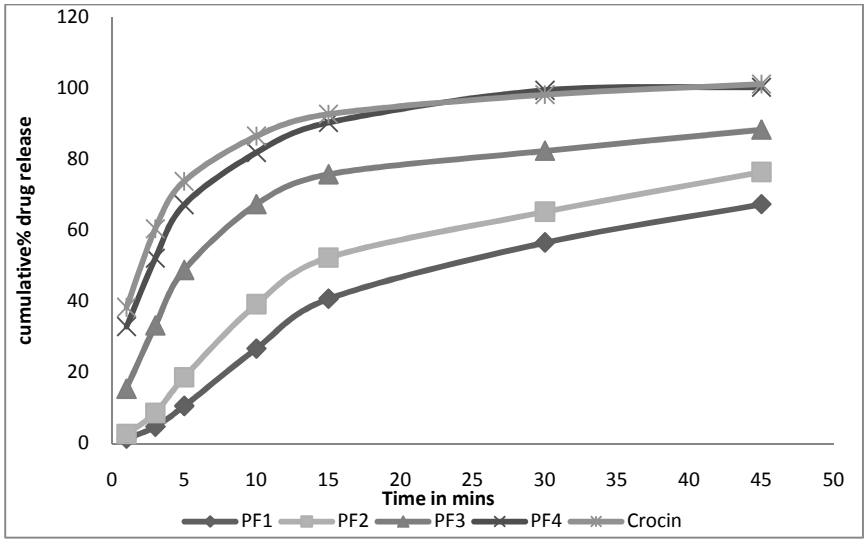


**Fig. 2: Dissolution profile of Paracetamol formulations against Crocin®**

**Table 2: Evaluation of paracetamol tablets**

| Evaluation test | PF1 | PF2 | PF3 | PF4 | Crocin® |
|---|---|---|---|---|---|
| Weight variation | - | | - - | - | - |
| Friability | 1.02% | 2.76% | 0.25% | 0.13% | 0.19% |
| Disintegrating time | 12.2mins | 10.3mins | 4.5mins | 2.8mins | 2.4mins |
| Dissolution time t60 | 35.7mins | 24.5mins | 7.8mins | 4.9mins | 4.1mins |

– Within limits of variation; n=20 tablets subjected for test.

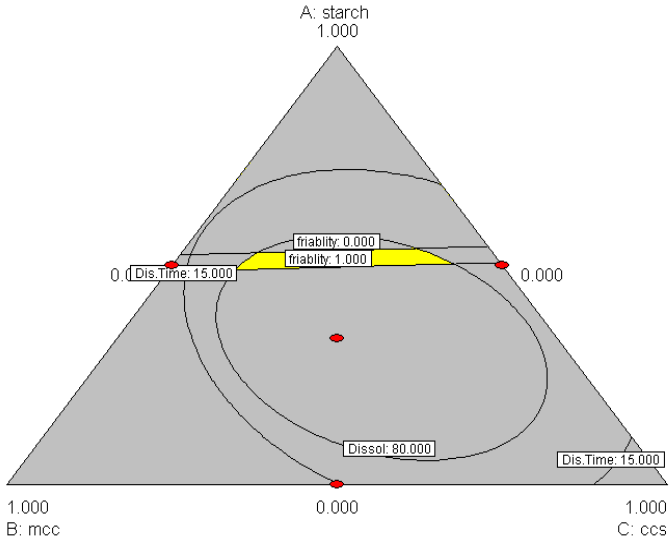


**Fig. 3: Contour graph showing the design space and the output for the experiment**

**Table 3: Formulations of diclofenac sodium sustain release granules**

| Ingredients | DF1 (mg) | DF2 (mg) | DF3 (mg) | DF4 (mg) | DF5 (mg) | DF6 (mg) |
|---|---|---|---|---|---|---|
| Diclofenac sodium | 100 | 100 | 100 | 100 | 100 | 100 |
| HPMC | 90 | 85 | 80 | 75 | 70 | 65 |
| Lactose | 45 | 45 | 45 | 45 | 45 | 45 |
| Talc | 0.5 | 0.5 | 0.5 | 0.5 | 0.50 | 0.5 |
| Magnesium stearate | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |

n=20 tablets subjected for test.

**Table 4: Evaluation of diclofenac sodium tablets**

| Evaluation test | DF1 | DF2 | DF3 | DF4 | DF5 | DF6 | Voveran® |
|---|---|---|---|---|---|---|---|
| Weight variation | - | - | - | - | - | - | - |
| Friability | 0.10% | 0.25% | 0.43% | 0.39% | 0.57% | 0.41% | 0.73% |
| Dissolution time t60 | 10 hrs | 8.6hrs | 7.5hrs | 6.5hrs | 5.8hrs | 5hrs | 5.7hrs |
| Higuchi model regression value | 0.834 | 0.885 | 0.864 | 0.984 | 0.932 | 0.917 | 0.991 |

-within limits of variation; n=20 tablets subjected for test.

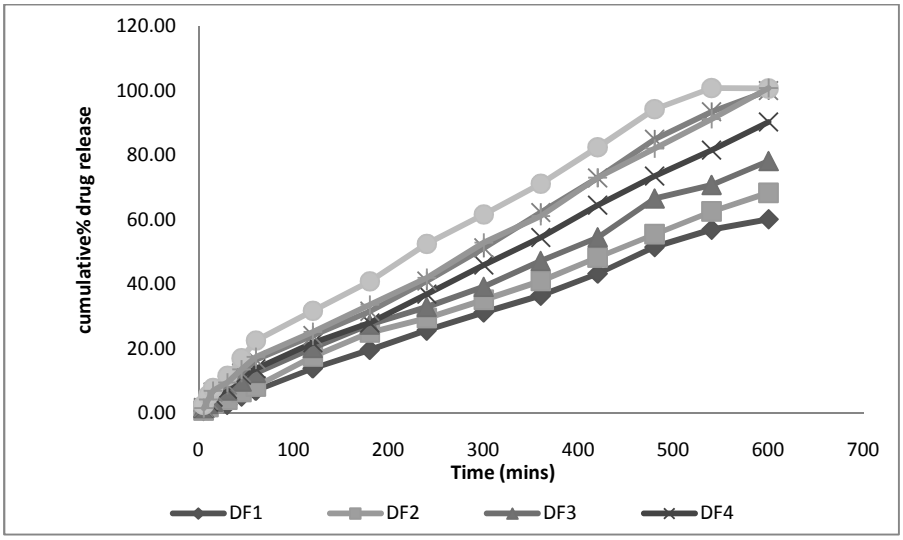


**Fig. 4: Dissolution profile of Diclofenac sodium extended release formulation against Voveran®**

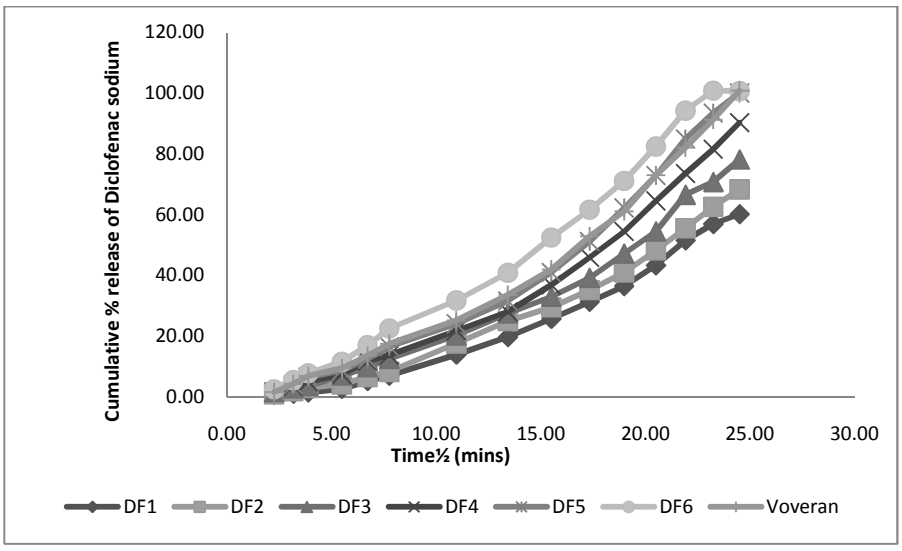


**Fig. 5: Dissolution profile of Diclofenac sodium extended release formulation against Voveran® (Higuchi Model)**

**Preparation of bilayer tablets**

For the preparation of bilayer tablets the optimized batch of paracetamol and diclofenac sodium were taken. Bilayer tablet press (Karunavathi&Co.) with D tooling of punch size 19.2mm was used. The first layer was sustained release diclofenac sodium and second layer was conventional release paracetamol. Then the tablets were evaluated for weight variation, friability, hardness, and invitro dissolution[14, 15].

**Evaluation**

The invitro evaluation studies were conducted on the bilayer tablets. Weight variation was done for 20 tablets and ±5% variation is applied as the average weight is above 500 mg. Friability was done for 20 tablets and the limit was ≤ 1%.

**Dissolution profiling**

The dissolution was carried out with distilled water pH 7.2 in USP apparatus II (Electrolab TDT-08L). The operation parameters are as follows rpm 100, temperature 37.5°C, bath volume 1000 mL and sampling interval are 5, 10, 15, 30, 45, 60, 120, 180, 240, 300, 360, 420, 480 mins. The percentage release was estimated by simultaneous estimation with UV spectrometer followed by Q analysis.

**Determination of isobestic point & selection of wavelength**

A double beam UV-Visible spectrophotometer model (Analytical instruments) having quartz cell of 1cm±0.5 light path length is used. Standard stock solution 100µg/mL of paracetamol and diclofenac sodium was prepared by dissolving separately, 10mg of drug made up to100mL with water, and then 25mL from stock is made up to 100mL to get 25µg/mL The λmax of paracetamol and diclofenac sodium were calculated by scanning in 200nm to 400nm UV range using 25µg/mL concentration. Then both the spectrum, i.e. paracetamol and diclofenac sodium were used to find isobestic point. The wavelengths at which absorbance values was same represent an isobestic point provide that both solutions should have same concentration. The λmax of paracetamol was found to be 243nm and diclofenac sodium was to be 276nm and the isobestic point was to found as 265nm. At 265nm paracetamol and diclofenac sodium of same concentration had same absorbance. The mixture is prepared by pipetting paracetamol and diclofenac sodium, each 25ml from standard stock solution and make up to 100ml with distilled water. Note the absorbance at isobestic point. This method of analysis is based on the absorption of drug paracetamol and diclofenac sodium, the quantification analysis was performed by using equation 1 and equation 2[16].

Equation -1,

$$Cx = [(Qm-Q1)/(Q2-Q1)] \times (A/a)$$

Equation -2

$$Cy = [(Qm-Q1)/(Q1-Q2)] \times (A/a)$$

Where,

$C_x$ and $C_y$ - the concentrations of paracetamol and diclofenac sodium.

Qm - absorbance of mixture of paracetamol and diclofenac sodium at isobestic point λmax to any of one component.

Q1 - Absorbance ratio of paracetamol.

Q2 - Absorbance ratio of diclofenac sodium.

A - Absorbance of mixture at isobestic point.

a - Absorptivity value of mixture at isobestic point.

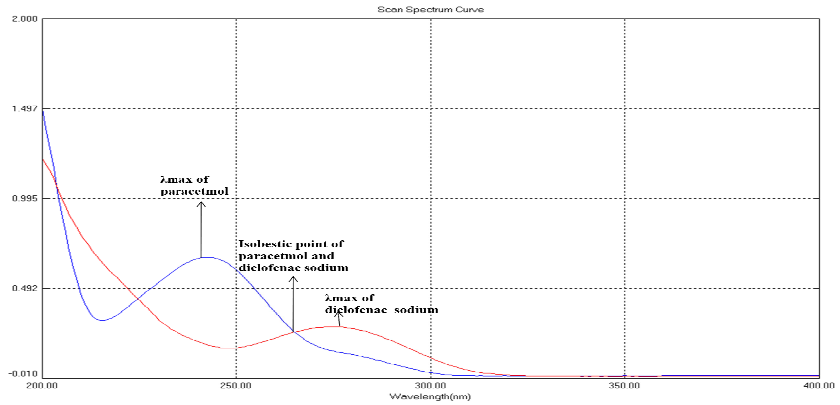


**Fig. 6: Overlain spectra Diclofenac (-----) and Paracetamol (-----), Iso-absorptive point (265.0nm)**

**Table 5: Intraday, interday, LOQ and LOD data**

| Drug | Intraday precision* %COV | Interday precision* % COV | | | LOD(µg/mL) | LOQ(µg/mL) |
|---|---|---|---|---|---|---|
| | | Day 1 | Day 2 | Day 3 | | |
| Paracetamol | 0.133 | 0.149 | 0.139 | 0.156 | 0.198 | 0.892 |
| Diclofenac sodium | 0.295 | 0.245 | 0.285 | 0.299 | 0.229 | 0.592 |

*mean of six determination, COV is coefficient of variance, LOD is lower limit of detection, LOQ is lower limit of quantification.

**RESULTS AND DISCUSSION**

Simultaneous estimation method of paracetamol and diclofenac was done by absorption ratio method. The prepared bilayer tablets were compared against the standard drug formulation in market. Crocin® was made as standard against paracetamol conventional release and voveran® was made as standard against sustain release diclofenac sodium.

The dissolution profile compared by adding voveran® and crocin® in same jar of dissolution media. Then at each sampling point, both the sample and standard were collected. The dissolution profiles of paracetamol, diclofenac and marketed products have great correlation.

The simultaneous estimation method used has great sensitivity for both the drugs. The lower limit of deduction was found to be 0.198(µg/mL) and 0.229(µg/mL) for paracetamol and diclofenac sodium respectively. The lower limit of quantification was found to be 0.892(µg/mL) and 0.592(µg/mL) for paracetamol and diclofenac sodium respectively. The interday and intraday precisions are found for 6 samples determination and it was found to be consistent. Interday precision was found for 3 days for consistent results[17].

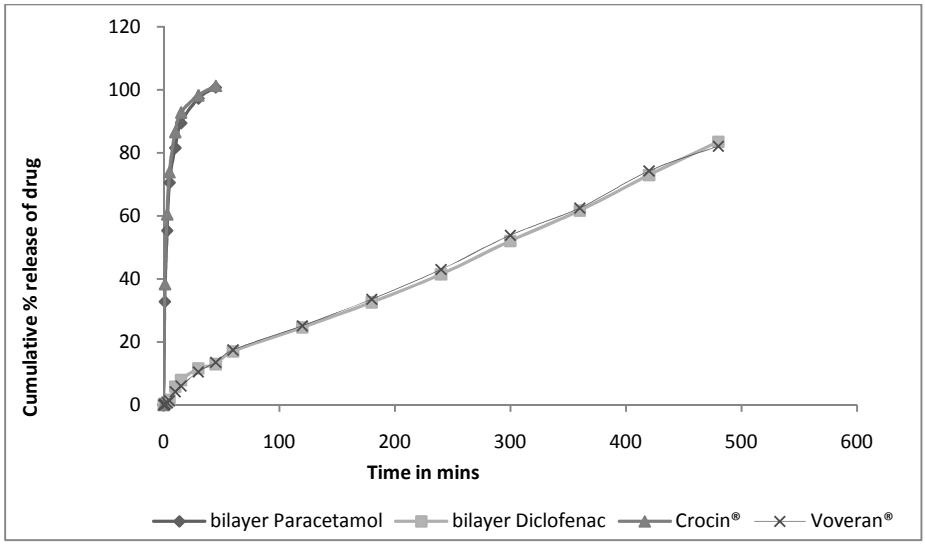


**Fig. 7: Dissolution profile of Bilayer tablet (Paracetamol and sustain release Diclofenac), Crocin® and Voveran®**

## CONCLUSION

The dissolution profiling of bilayer tablet done by simultaneous estimation method was efficient and accurate. The formulations PF4 and DF4 release patterns were found to be similar to marketed product. By this type of formulations patient compliance will increase due to overcoming problems like dose missing, frequency of dosing. The spectrophotometric method was validated and showed to be specific, linear, precise and accurate.

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