

## Research Article

## Comparative Study on Ulcerogenicity and Anti-Inflammatory Activities of Pure Aceclofenac with the Aceclofenac Loaded Interpenetrating Polymer Network (IPN) Beads in Rats

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### ABSTRACT

Aceclofenac is non steroidal anti-inflammatory drug (NSAID) used for relief of pain and inflammation in osteoarthritis, rheumatoid arthritis and ankylosing spondylitis. It is however commonly associated with side effects including high incidence of duodenal and gastric ulceration, gastrointestinal bleeding, peptic ulceration and perforation. The objective of the present study was to evaluate and compare the ulcerogenic effect and the anti-inflammatory effect of Aceclofenac loaded Interpenetrating Polymer Network (IPN) beads developed by cross linking Sodium Carboxymethyl Xanthan (SCMX) and Sodium Carboxymethyl Cellulose (SCMC) using aluminium chloride (AlCl<sub>3</sub>) as cross linking agent with that of pure Aceclofenac in 150-200 g weight adult albino Wistar rats (Male and Female). The present study Results indicate that ulcerogenicity decreases significantly with Aceclofenac loaded Interpenetrating Network Polymer (IPN) beads in comparison to the pure Aceclofenac and also increasing the anti-inflammatory property.

**Keywords:** Ulcerogenicity, Anti-inflammatory, IPN, Cross-link, Polymer.

### INTRODUCTION

The treatment of inflammation and pain is an important area of clinical science. In the last decade, non steroidal anti-inflammatory drugs (NSAIDs) have played a central role in these indications and they are currently considered as the first choice, being one of the most widely prescribed drugs<sup>1,2</sup>. Aceclofenac is a phenyl acetic acid derivative, having potent analgesic & anti-inflammatory property<sup>3</sup>. The effect of NSAIDs is mediated to large extent by inhibition of prostaglandin synthesis through cyclooxygenase (COX) enzyme. COX has two isoenzymes in humans: COX-1 has cytoprotective function in the gastric mucosa and COX-2 is detected in several tissues when an inflammatory reaction takes place<sup>4</sup>. NSAIDs have been demonstrated to inhibit COX-2 activity and suppress the prostaglandin E<sub>2</sub> production by inflammatory cells<sup>5</sup> NSAIDs are well

accepted as a therapy for a variety of chronic arthritis pain syndromes and inflammatory conditions, most commonly rheumatoid arthritis and osteoarthritis<sup>6,7</sup>.

In case of rheumatoid arthritis and osteoarthritis, where patients generally remember morning and evening medication but tend to forget doses in between, thus leading inaccurate dosing or coverage<sup>8</sup>. One or two daily doses improve therapy by maintaining steady state plasma concentration as well as the troughs of low plasma concentration<sup>9</sup>. Use of this drug by patients has become restricted because of its adverse complication, particularly to the gastrointestinal system<sup>10</sup>. Controlled release or sustained release formulations with non irritant bio-compatible polymers not only provide the protection to the gastrointestinal tract (GIT) but also used in the treatment of osteoarthritis, rheumatoid arthritis and other joint pains. Generally

natural polymers like xanthan gum, gellan gum, sodium alginate are used for because of their biocompatibility and capacity to absorb large quantities biological fluid or water<sup>11-13</sup>. Beads prepared by cross linking a homopolymer or heteropolymer gives rise to sustained release formulation, release from which can be modulated as per requirement by varying extent of cross links. Aceclofenac loaded Interpenetrating Polymer Network (IPN) beads has been formulated to reduce gastrointestinal tract irritation and to release the drug for prolong period. The controlled release formulation of Aceclofenac loaded IPN bead has the potential to minimize its toxicity and extend the duration of pharmacological efficacy. The present study has been designed to know whether the formulation shows better anti-inflammatory activity and reduces the ulcerogenic property.

## MATERIALS & METHODS

### Chemicals and Reagent

Aceclofenac (Indian Pharmacopoeia) were gift sample from Karnataka Antibiotics & Pharmaceuticals Limited, Karnataka India. Sodium carboxymethyl xanthan, Sodium carboxymethyl cellulose (SD Fine Chem Pvt. Ltd, Mumbai, India),  $AlCl_3 \cdot 6H_2O$  (Loba Chemie Pvt. Ltd, Mumbai, India), carrageenin (Spectrochem Pvt.Ltd.Mumbai./India), dextran and 5-HT (Sigma Aldrich<sup>®</sup>) and all other analytical grade reagents were obtained from different sources.

### Experimental Animals

Adult wistar albino rats, weighing (150-200g) were purchased from M/s BN Ghosh, Kolkata. The animals were feed a normal laboratory pellet diet and water *ad libitum*. They were housed in colony cages under standard laboratory conditions (12:12h light and day cycle, temperature at  $25 \pm 2^\circ C$  and relative humidity at  $55 \pm 10\%$ ). Animals were allowed to acclimate for 7 days to the laboratory conditions before the commencement of experiments. The ethical clearance was obtained from Jadavpur University Ethical

Committee for using animal in the present study.

### Experimental Design

The pure drug (Aceclofenac), the Aceclofenac loaded IPN beads were suspended in 1% carboxy methyl cellulose (CMC). A required volume was administered orally by gavages with an Fr 8 x 23-inch feeding tube. Fasted rats that were deprived of food but not water for 24 hrs prior to experiment were used to assess the effect of Aceclofenac and IPN beads and CMC on gastric mucosa.

### Comparative Ulcer study of pure Aceclofenac with the Aceclofenac loaded IPN beads in adult Wistar albino rats

#### Preparation of Aceclofenac loaded IPN beads

Sodium carboxymethyl xanthan (SCMX) and sodium carboxymethyl cellulose (SCMC) were dissolved in deionized water with constant stirring until a homogeneous solution was formed. Required amount of ACF was added to the polymer solution and dispersed homogenously. The resulting dispersion was extruded through 21 G flat-tip hypodermic needle into  $AlCl_3$  solution and gelled for different periods of time. The beads were then collected by filtration, washed with deionized water, dried at  $45^\circ C$  into a hot air oven to constant weight, and kept in a desiccator until used. The beads were prepared using the following variables:

Keeping the drug load constant at 20% w/w of total polymer,  $AlCl_3$  concentration at 2% w/v, gelation time at 0.5 h and total polymer concentration at 2.5% w/v, the weight ratio of SCMX: SCMC ratio was 50:50.

#### In-vivo ulcerogenicity study

Ulcerogenicity studies were conducted according to the reported procedures<sup>14-17</sup>. Adult Wistar albino rats fasted for 24 hrs but provided water *ad libitum* were randomly divided into four groups, each containing 6 animals.

The first group A received a suspension of 1% CMC, while group B and group C were

respectively pure Aceclofenac and aceclofenac-loaded IPN beads suspended in 1 ml 1% CMC suspension. After oral administration of the suspensions, all animals were kept for 6 hours and then sacrificed. The stomachs of sacrificed animals were removed and opened

through their greater curvature. Ulcer formations were examined under the microscope. The severity of mucosal damages was assessed by modification of a rating scale [18]. The rating scale used was as follows:

Observation	Score
No lesions:	0.0
Punctiform lesions (< 1 mm):	1.0
Five or more punctiform lesions:	2.0
One to five small ulcers (1-2 mm):	3.0
More than five small ulcers or one large ulcer:	4.0
More than one large ulcer (greater than 4 mm):	5.0

Based on the severity of mucosal damage, each specimen was assigned a score. The scores were averaged and the mean score was tabulated as the severity index for the drug and for the formulated drug suspension. Statistical significance ( $P < 0.01$ ) was performed by Dunnett's tests (GraphPad prism3 software) to test the significance of difference in the severity index between aceclofenac and aceclofenac loaded IPN beads.

#### **Comparative study of Anti-inflammatory activities of aceclofenac and the aceclofenac loaded IPN Beads in adult Wistar albino rats:**

##### **Carrageenin induced rat paw edema model**

This model was based on the principle of release of various inflammatory mediators by carrageenin[19]. The adult Wistar albino rats ( $n=6$ ) were divided into three groups. The first group received 1ml CMC (1%). The second group received the suspension of pure Aceclofenac (10mg/kg bw) in 1ml 1% CMC and the last group received suspension of Aceclofenac beads (55mg/kg bw, equivalent to 10 mg/kg bw pure Aceclofenac) orally.

The right hind paw was marked with the marker at the level of lateral melleolus. The basal paw volume was measured by volume displacement method using Plethysmometer by immersing the paw up

to the mark at the level of lateral malleolus. One hour after dosing, 0.1 ml of 1.0 % carrageenin was injected into the right hind paw of each rat. The paw volume was measured again at 1, 2, 3, 4 and 5 hours after challenge. The increase in paw volume was calculated as percentage compared with the basal volume. The percentage of inhibition was calculated using the following formula:

$$\% \text{ Inhibition} = \frac{V_c - V_t}{V_c} \times 100$$

Where  $V_c$  and  $V_t$  represent average paw volume of control and treated animals respectively.

##### **Dextran induced rat paw edema model**

The animals were treated exactly the same way as in the carrageenin-induced paw edema model but instead of carrageenin, here 0.1 mL of Dextran (1%w/v in normal saline) was used as the edemogen[20]. The paw edema was measured as mentioned in the carrageenin-induced paw edema model.

##### **Histamine-induced paw edema in rats**

Histamine-induced paw edema was studied using the same method which was used to determine the carrageenan induced paw edema. 0.1 ml of a 1.0% solution of histamine was administered into the sub-plantar side of the right hind

paws. The paw volume was measured time to time. The percentage of inhibition of the inflammation was calculated using the same formula that has been given above and compared with the normal group [21]

## RESULTS AND DISCUSSION

### Evaluation of In-vivo Ulcerogenicity study

Gastric and Duodenal ulceration caused by NSAIDs can be guarded by incorporating the drug in a polymer matrix [22]. There has been increase in the design of a drug delivery system containing NSAIDs loaded microparticles or microspheres [23].

The analgesic, anti-inflammatory and ulcerogenic effects of solid dispersion of Meloxicam in polyvinylpyrrolidone and polyethylene glycol 6000 and of their physical mixture have been compared with pure Meloxicam. The results have shown that the solid dispersion and physical mixture possess better effect with reduced ulcer activity when compared with pure Meloxicam [24]. It was also found that the severity of ulceration could be related with formulation design and drug release kinetics [25].

In the ulcerogenic study, gastric mucosal injuries were evaluated by examining the stomach tissues rat treated with placebo of (CMC), pure aceclofenac and aceclofenac loaded IPN beads. Its results have been shown respectively in figure 1 A, figure 1 B and figure 1 C. Comparative ulcer-index results have been shown in (Table-1).

Mucosal damage was found in pure aceclofenac and aceclofenac loaded IPN beads treated stomach of the sacrificed animals (Figures 1B and 1C). No haemorrhaging surface was noted in the group treated with CMC suspension (Figure 1A). The severity of ulcer-index was measured on a rating scale. On the basis of rating scale the ulcer index the animals treated with pure aceclofenac was  $3.333 \pm 0.84$  and that of the animals treated with aceclofenac loaded IPN beads was found to be  $1.5 \pm 0.71$ .

The observed data clearly indicate that the aceclofenac-loaded IPN beads have the potential to reduce its ulcerogenic effect compared to pure aceclofenac.

### Evaluation of Anti inflammatory study

In order to have a better comparison between the anti-inflammatory activity of aceclofenac and aceclofenac loaded IPN beads, evaluation was made on the basis of their ability to inhibit the oedema produced in hind paw of rats after challenging with the carrageenan, dextran & histamine.

The results for evaluation of anti-inflammatory effect of aceclofenac, aceclofenac loaded IPN beads, carrageenan, dextran and histamine induced oedema have been shown respectively in Figure 2, Figure 3 and Figure 4 respectively.

Change in carrageenan induced paw volume of rats following administration of 1% CMC suspension (Placebo), pure aceclofenac and aceclofenac loaded IPN beads have been represented in (Table 2). When 1% CMC was administered, the increase in paw volume was  $(0.37 \pm 0.007)$  ml at first hour. With time, the increase in paw volume increased up to 4<sup>th</sup> hour and then decreased. Following administration of pure aceclofenac at a dose of 10mg/kg body wt, the change in paw volume with time followed the same pattern as that exhibited by the placebo. However, the increase in paw volume at each time measured was considerably less than that produced by the placebo.

On the other hand, the increase in paw volume following administration of aceclofenac loaded IPN beads was slightly higher than that produced by the pure drug. However, the change in paw volume with time followed the same pattern. Similar results were observed in the changes in Dextrin (Table 3) and histamine (Table 4) induced paw volume following administration of 1% CMC, aceclofenac and aceclofenac loaded IPN beads.

In case of carrageenan challenge, the inhibition of edema produced by aceclofenac was 37.9% at 1st hour,

increased to 54.6% at 5<sup>th</sup> hour. On the other hand, though the percentage inhibition produced by aceclofenac loaded IPN beads was less than that produced by pure aceclofenac up to about 3<sup>rd</sup> hour, it increased steady up to 5<sup>th</sup> hour (**Figure-2**). Similar observations were found against the dextran (**Figure-3**) and histamine (**Figure-4**) challenge.

Pure Aceclofenac inhibits the paw oedema volume but to a lesser extent, on the other hand the inhibitory or anti-inflammatory effect produced by aceclofenac loaded IPN beads was found over a long period of time.

**Table 1: A comparative Ulcer study of CMC, Pure Aceclofenac and Aceclofenac loaded IPN beads**

Group	Dose	Ulcer-index
Contrl (CMC)	1ml 1%	0.00
Raw/Pure Aceclofenac	10mg/Kg bw	3.333±0.84*
Aceclofenac loaded IPN beads	55mg/Kg bw**	1.5±0.71*

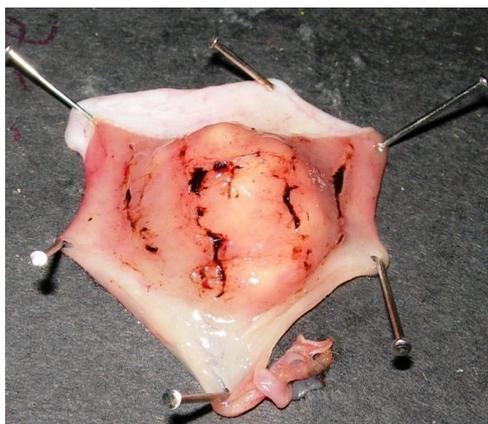
\*P<0.01 when all treated groups are compared with CMC group.

\*\*55 mg/Kg bw of Aceclofenac loaded IPN bead is equivalent to 10mg/Kg bw of Pure Aceclofenac. Values are expressed as mean±SEM for six independent observations (n=6).

Statistical differences were determined by ANOVA followed by Dunnett's test.



**Fig. 1A: Ulcerogenicity effect of Control (CMC) treated rat**



**Fig. 1B: Ulcerogenicity effect of Pure/Raw Aceclofenac treated rat**



**Fig. 1C : Ulcerogenicity effect of Aceclofenac loaded IPN beads treated rat**

Groups	Dose	Mean increase in paw volume (mL)					
		0 hr (initial paw volume)	1hr	2 hr	3hr	4hr	5hr
Control (CMC)	1ml (1%)	0.00	0.37±0.007	0.49±0.015	0.65±0.01	0.71±0.01	0.63±0.007
Raw/Pure Aceclofenac	10mg/kg bw	0.00	0.23±0.007* (37.89)	0.24±0.008* (50.51)	0.25±0.01* (60.76)	0.29±0.007* (58.84)	0.28±0.009* (54.59)
Aceclofenac loaded IPN Beads	55mg/kg bw**	0.00	0.25±0.008* (33.04)	0.26±0.007* (46.78)	0.27±0.006* (58.48)	0.28±0.005* (60.9)	0.23±0.001* (62.72)

**Table 2: Anti-inflammatory effect of Raw Aceclofenac and Aceclofenac loaded IPN beads on carrageenin induced rat paw edema**

\*P<0.01 when all treated groups are compared with Control (CMC) group and the value indicate paw volume in rats.

\*\*55 mg/Kg BW of Aceclofenac loaded IPN bead is equivalent to 10mg/Kg bw of Raw Aceclofenac. Values are expressed as mean±SEM for six independent observations (n=6). The data within the bracket indicate the percentage inhibition value. Statistical differences were determined by ANOVA followed by Dunnett's test.

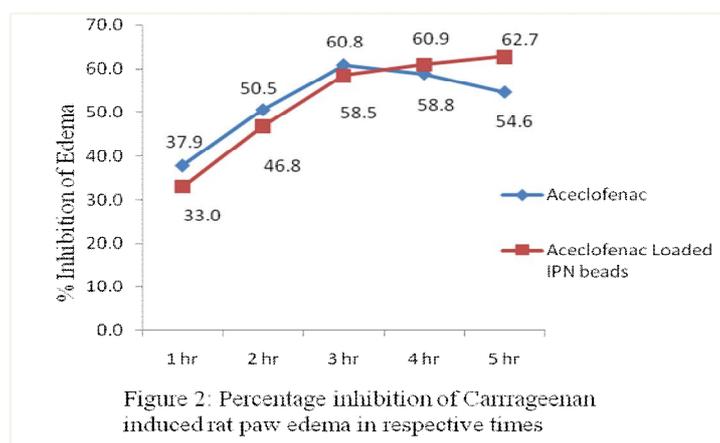


Figure 2: Percentage inhibition of Carrageenan induced rat paw edema in respective times

**Table 3: Anti-inflammatory effect of Raw Aceclofenac and Aceclofenac loaded IPN beads on Dextran induced rat paw edema**

Groups	Dose	Mean increase in paw volume (mL)					
		0 hr (initial paw volume)	1 hr	2 hr	3 hr	4 hr	5 hr
Control (CMC)	1ml (1%)	0.00	0.34±0.010	0.43±0.017	0.64±0.015	0.70±0.014	0.60±0.016
Raw /Pure Aceclofenac	10mg/kg bw	0.00	0.21±0.009* (37.74)	0.23±0.006* (46.15)	0.24±0.011* (62.17)	0.29±0.011* (58.72)	0.27±0.010* (54.26)
Aceclofenac loaded IPN Beads	55mg/kg bw**	0.00	0.23±0.006* (31.37)	0.25±0.007* (41.15)	0.26±0.010* (59.32)	0.27±0.013* (61.55)	0.22±0.008* (63.08)

\*P<0.01 when all treated groups are compared with CMC group and the value indicate paw volume in rats.

\*\*55mg/Kg bw of Aceclofenac loaded IPN bead is equivalent to 10mg/Kg bw of Raw Aceclofenac. Values are expressed as mean±SEM for six independent observations (n=6). The data within the bracket indicate the percentage inhibition value. Statistical differences were determined by ANOVA followed by Dunnett's test.

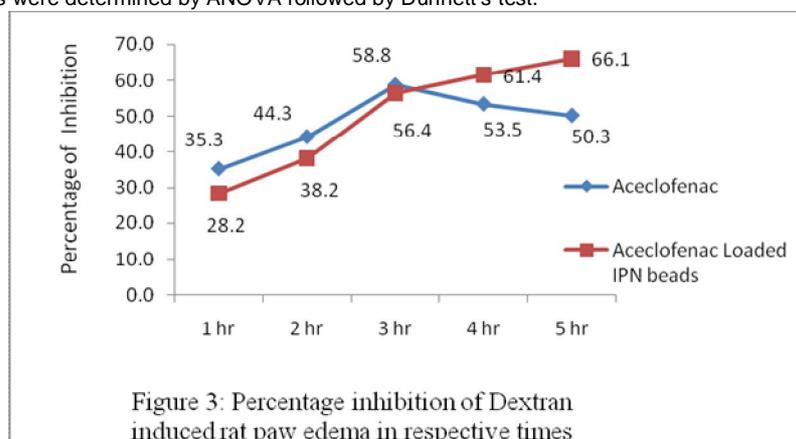


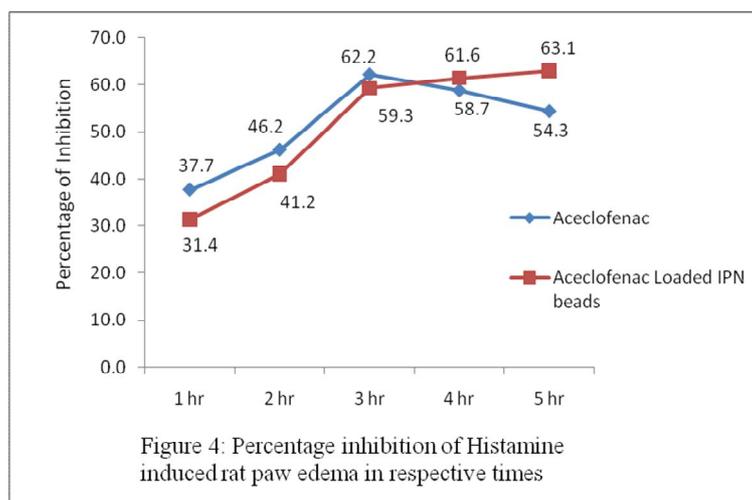
Figure 3: Percentage inhibition of Dextran induced rat paw edema in respective times

**Table 4: Anti-inflammatory effect of Raw Aceclofenac and Aceclofenac loaded IPN beads on Histamine induced rat paw edema**

Groups	Dose	Mean increase in paw volume (mL)					
		0 hr (initial paw volume)	1 hr	2 hr	3 hr	4 hr	5 hr
Control (CMC)	1ml (1%)	0.00	0.26±0.009	0.38±0.007	0.57±0.02	0.64±0.009	0.60±0.018
Raw /Pure Aceclofenac	10mg/kg bw	0.00	0.16±0.006* (35.25)	0.21±0.007* (44.29)	0.23±0.007* (58.77)	0.30±0.01* (53.47)	0.29±0.009* (50.27)
Aceclofenac loaded IPN Beads	55mg/kg bw**	0.00	0.18±0.01* (28.20)	0.23±0.005* (38.15)	0.24±0.011* (56.43)	0.25±0.009* (61.43)	0.20±0.006* (66.11)

\* $P < 0.01$  when all treated groups are compared with CMC group and the value indicate paw volume in rats.

\*\*55 mg/Kg BW of Aceclofenac loaded IPN bead is equivalent to 10mg/Kg BW of Raw Aceclofenac. Values are expressed as mean  $\pm$  SEM for six independent observations (n=6). The data within the bracket indicate the percentage inhibition value. Statistical differences were determined by ANOVA followed by Dunnett's test.



## CONCLUSION

From the studies it is concluded that the aceclofenac loaded IPN beads provide better beneficial effects in the management of inflammation with reduced ulcer

occurrences. So the aceclofenac loaded IPN beads provide prolonged anti-inflammatory activity and less side effects compared to raw aceclofenac.

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