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Original Research Article

IN-VITRO AND IN-VIVO CHARACTRIZATION OF FLURBIPROFEN NANOGEL DRUG DELIVERY SYSTEM

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Abstract: The main objective of present work is in-vitro and in-vivo characterization of flurbiprofen nanogel drug delivery system. The drug release from flurbiprofen nanogel was determined using through Franz diffusion cell in buffer. Injection of carrageenan into the hind paw induced a progressive edema reaching its maximum at 3 hours. For determination of paw volume animal divided into Group-I to VI, each group show different value. These values were found to be statistically significant at $P<0.05$. Carrageenan administration resulted in significant higher weight of tissue punch (174.67 ± 1.23) mg after 24 hr, as compare to control group (104.53 ± 1.21) mg. Standard drug celecoxib treated group-III showed significant weight decrease (107.43 ± 1.4) mg as compare to Group-II and inflammation reduced similar to control group. Drug flurbiprofen treated group-IV showed significant weight decrease (152.65 ± 1.02) mg as compare to Group-II, and inflammation reduced but not as the standard drug celecoxib treated Group-III. Carrageenan administration resulted in significant higher percentage (%) difference in weight 40.156 % after 24 H, as compare to control Group-I. Percentage (%) difference in weight was observed. It means higher percentage of inflammation reduced by nanogels other than standard drug.

Keywords: Inflammation, Mechanism, Evaluation, Tissue, Drug.

INTRODUCTION

Inflammation is a defensive mechanism in the body the immune system recognized damaged cells, irritant, and pathogens and protective response involving immune cell, blood vessel that serves as a mechanism initiating the elimination of noxious agent and of damage tissue inflammation is part of body's immune response. Inflammation disorder for ex-Autoimmune diseases, inflammatory bowel disease, acne vulgaris, Treatment of inflammation are NSAIDs drugs are usually first line of defenses in treating short term pain, inflammation (aspirin, ibuprofen, and naproxen) corticosteroids (predenisone) [1].

The five classical signs of inflammationare heat, pain, redness, swelling, and lossof function (Latin calor, dolor, rubor, tumor, and functionl area). Inflammation is the mechanism of human diseases displaying the five classic inflammatory signs: redness, swelling, heat, pain and subsequent loss of organ function. The inflammatory state was also defined as "lesion of the vessels which are attacked by the irritating cause." Depending on the nature of the "irritating cause," distinguish the following types of inflammation: microbial, autoimmune, allergic, metabolic and physical inflammation displayed such as heat, pain, redness, Swelling in infected or injured tissues, It occurs as blood vessels in response to damage, Immobility. The inflammatory process is intended to inactivate and remove the injury agent, as well as to remove any

damaged tissue caused by the injury and to aid in repair and healing.

Cause of Inflammation[4]

Physical Causes: Physical injury, blunt or penetrating**,** Mechanical trauma**,** Burns**,** Radiation.

Biological Causes: Infection by pathogens, Immune reactions due to hypersensitivity, Stress.

Chemical Causes: Toxins, Alcohol, Psychology, All painful or chronically harmful disease needing pharmacological treatment. All the steroidal and non-steroidal anti-inflammatory drugs (NSAID) which have been used since the introduction of acetyl salicylic acid.

1.1.2 Type of Inflammation:

Inflammation has been classified in to two major types:

(a) Acute inflammation: Acute inflammation is a short term process occurring in response to tissue injury. Acute inflammation is felt within about 0.1 second after pain stimuli is applied acute pain is also describe by many alternate names such as sharp pain ,pricking pain, fast pain,electric pain[5]. It involves a coordinated andsystemic mobilization response locally ofvarious immune, endocrine and neurolological mediators of acute inflammation. In a normal healthy response, it becomesactivated, clears the pathogen and beginsa repair process and then ceases. Acute inflammation is the initial response of the body to harmful stimuli and is achieved by theincreased movement of plasma and leukocytes from the blood into the injured tissue.A series ofbiochemical events propagates and mature the inflammatory response involving the local syatem the immune system and various cells within injured tissue such as acute bronchitis, a scratch or cut on the skin, tonsillitis

(b) Chronic inflammation: Chronic inflammation refers to a prolonged inflammatory response that involves a progressive change in the type of cells present at the site of inflammation an autoimmune disorder that attack normal healthy tissue, mistaking it for pathogen that causes disease[6].Chronic inflammation can continue for month or years. It either has or may have links to various diseases such as asthma, tuberculosis, chronic peptic ulcer, diabetes , allergic, cardiovascular disease

Mechanism of inflammation: Arachidonic acid is a polyunsaturated fatty acid covalently bound in estrified from in the cell membrane of most body cells. Arachidonic acid is released and oxygenated by enzyme system leading to the formation of an important group of inflammatory mediators. Arachidonic acid metabolism occurs in 5- lipoxygease pathway which produces a collection of leukotrienes (LT), second cyclooxygenase (COX) pathway which produces prostaglandin H2 (PGH2).

Advantages of Nanogels

- Highly biocompatible (due to high watercontent and hence behave like natural tissue) and therefore immunological responses
- Biodegradable, that makes thesenanocarriers nontoxic
- High drug loading capacity
- Easily escape entrapmentby reticuloendothelial system
- By tuning crosslinking densities drug release can be regulated

MATERIAL AND METHODS

In-vitro drug release study using Franz diffusion cell: The drug release from nanogel was determined using dialysis bag through Franz diffusion cell in buffer. The diffusion media of receptor compartment was continuously stirred on magnetic stirrer kept at a temperature of 37 ± 0.5 °C. Samples (1 ml each) were withdrawn from the release medium at 10, 15, 20, 30, 40, 50, 60 min and replaced with an equal volume of fresh buffer solution to maintain sink conditions. The amount of drug released from the nanogel was determined by UV spectrophotometer. The result of % cumulative drug release (% CDR) are shown in the tables.

Biological evaluation of prepared optimized formulations

Animals care and Handling: The animal experimental protocol was approved by the Institutional Animals Ethical Committee (IAEC), Bhopal, (M.P). Approval Number is **Ref/05/IAEC/Pharmacy/2024,** date **20/04/2024**. Male & female Wistar albino rats (200-250g) were provided by Institution, Bhopal Madhya Pradesh, India. The animals were housed in standard conditions of temperature (25±2^{O}C) and 12:12 h light-dark cycle. The rats were fed with commercial diet and water *ad Libitum*.The experiment was approved by the Institutional Ethics Committee, (M. P.).

In-vivo anti-inflammatory activities determination

Paw edema induction: Healthy animal will be selected, randomized based are body weight and divided into 6 different groups containing of 6 animals each. Before starting the experiment animals will be housed for 14 days in controlled environment. Edema was produced by injecting 0.1 ml of a solution of 1% Carrageenan in the left hind paw. Topically applied saline as control, pure drug (celecoxib) dispersed in saline was applied as positive control and topically optimized Nanoegels was given for testing.

(B) Assay procedure:

- Male albino rats weighing 200-250g kept at room temperature in a light controlled animal house. Animals were fasted with free access to water at least 12 h prior to the experiments.
- The 1% carrageenan solution was prepared in 0.9% normal saline. Pure drug (celecoxib and flurbiprofen) dispersed in normal saline.
- The total 36 animals were divided into 6 groups, each group having six animals. Plantar

of right hind paw was clean using 70% alcohol before injection. Normal control group-I was injected normal saline in right hind paw.

- Group-II to Group-VI wasinducededema by injection of 0.1 ml of a solution of 1% carrageenan in right the hind pawsub-plantar surface. One hour before the injection of carrageenan, Group-III was applied standard drug celecoxib dispersion in saline.
- One hour before the injection of carrageenan, Group-IV was applied standard drug flurbiprofen dispersion in saline. One hour before the injection of carrageenan, Group-V was applied Nanogel **A5**.
- One hour before the injection of carrageenan, Group-V was applied Nanogel **B4**.
- Paw volume (ml) was measured by water displacement with a plethysmometer, 0.5 h, 1 h, 2 h, and 3 h after treatment with carrageenan. The percentage was calculated by the following equation:

Anti-inflammatory activity % = (1-D/C) x 100

Where, D represents the difference in paw volume before and after drug administration to the rats and C represents the difference of volume in the control groups.

- Animals were anesthetized.
- Tissue punch of 6mm diameter was collected for edema measurement and histology.

(D) Evaluation parameter:

- Paw volume was measured by water displacement with a plethysmometer, 0.5 h, 1 h, 2 h, and 3 h after treatment.
- The edema was measured by weights of the inflamed tissue punch.
- Histological Studies

(C) Experimental Design

Table No. 1: Experimental design and group distribution of animal

Groups	Treatment	Number of Animals
Group-I	Control (normal saline)	6
Group-II	Carrageenan only	6
Group-III	Carrageenan + standard drug	6
Group-IV	Carrageenan + pure flurbiprofen	6
Group-V	Carrageenan + formulation A5	6
Group-VI	Carrageenan + formulation B4	6

RESULTS AND DISCUSSION

In-vitro drug release study using Franz diffusion cell: The drug release from nanogel based topical spray was determined using Franz diffusion cell in buffer. The diffusion media of receptor compartment was continuously stirred on magnetic stirrer kept at a temperature of 37±0.5 °C. A 20 ml of nanogel dispersion was placed in diffusion cell. Samples (1 ml each) were withdrawn from release medium at 10, 15, 20, 30,40, 50, 60 min and replaced with an equal volume of fresh buffersolution to maintain sink conditions. Amount of drug released from nanogel was determined by UVspectrophotometer. The result of % cumulative drug release (%CDR) for nanogel dispersion are shown in the table. The drug release from nanogel was determined using Franz diffusion cell in buffer. The result of % cumulative drug release (%CDR) was found highest i.g. 88.91% for A-5.

Table No. 2: *In-vitro* drug Release Study of flurbiprofen loaded Nanogel

Time (min)	Cumulative % of drug release								
	A-1	A-2	A-3	A-4	A-5	A-6	A-7	A-8	A-9
0	00.00	00.00	00.00	00.00	00.00	00.00	00.00	00.00	00.00
10	10.00	11.07	09.22	07.73	23.83	18.92	16.73	17.28	18.26
15	18.02	17.92	17.83	12.02	35.84	27.83	25.81	26.38	28.16
20	27.37	26.03	29.75	21.86	47.17	32.73	33.32	35.38	37.37
30	31.84	32.92	36.72	33.83	59.12	41.24	40.52	46.72	48.42
40	39.07	37.12	45.31	49.76	70.16	48.27	47.61	51.68	53.37
50	46.28	41.83	52.73	56.81	82.62	53.74	53.41	55.62	58.38
60	49.73	45.27	68.72	66.18	88.91	55.32	56.34	57.73	62.15

(Where, n=3, mean ±**SD**)

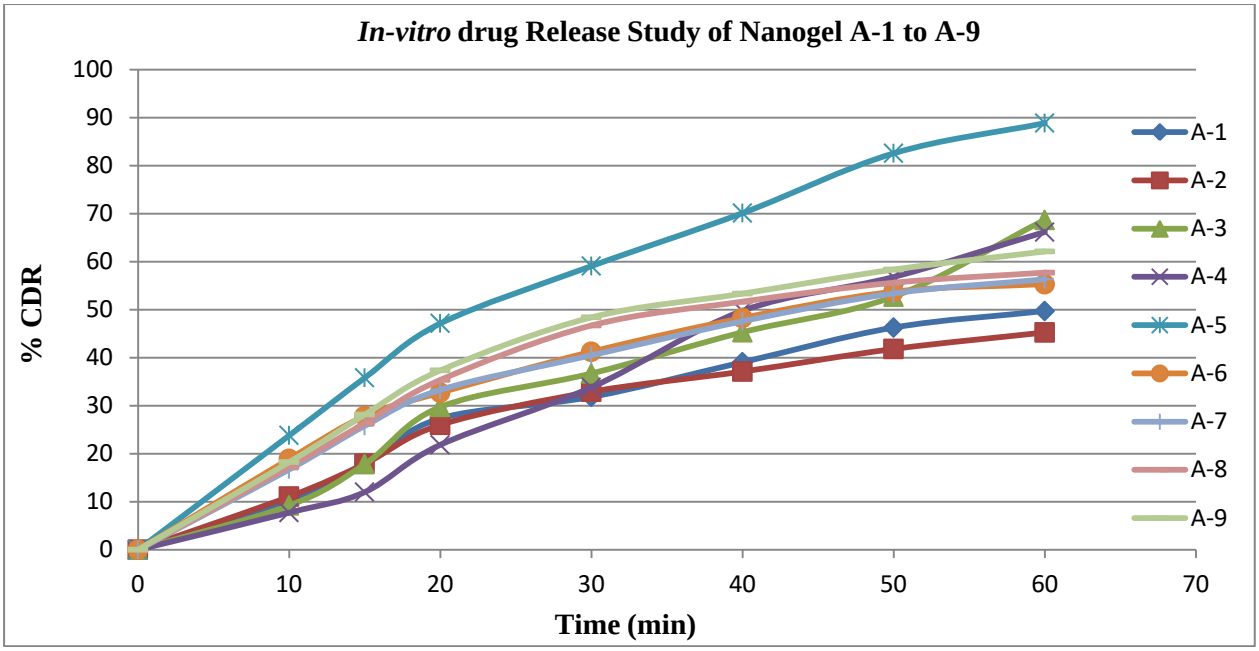

Figure 1 : *In-vitro* drug Release Study of Nanogel

In-vitro drug release study using Franz diffusion cell: The drug release from nanogel was determined using through Franz diffusion cell in buffer. The diffusion media of receptor compartment was continuously stirred on magnetic stirrer kept at a temperature of 37 ± 0.5 °C. A 20 ml of nanogel dispersion was placed in diffusion cell. Samples (1 ml each) were withdrawn from therelease medium at 10, 15, 20, 30,40, 50, 60 min and replaced with an equal volume of fresh buffer solution to maintain sink conditions. The amount of drug released from the nanogel was determined by UV spectrophotometer. The result of % cumulative drug release (% CDR) for nanogel are shown in the **table**.

Table No. 3: *In-vitro* drug Release Study offlurbiprofen loaded nanogels (HA-CH)

Time (min)	Cumulative % of drug release								
	B-1	**B-2**	**B-3**	**B-4**	**B-5**	**B-6**	**B-7**	**B-8**	**B-9**
0	00.00	00.00	00.00	00.00	00.00	00.00	00.00	00.00	00.00
10	23.73	21.75	25.76	34.54	32.38	30.81	28.91	27.71	25.82
15	31.92	29.54	31.47	39.03	37.61	36.78	34.72	33.71	32.63
20	38.71	38.65	39.83	48.92	42.73	40.72	40.62	39.52	38.61
30	45.72	42.76	47.75	57.92	57.24	48.92	46.23	44.62	43.74
40	52.13	49.74	51.54	67.84	65.62	54.72	51.82	50.62	49.22
50	57.21	55.87	59.76	74.23	71.62	60.27	56.12	55.23	54.73
60	60.43	58.62	70.52	**81.74**	74.51	63.82	60.62	58.27	57.36

(Where, n=3, mean ±**SD**)

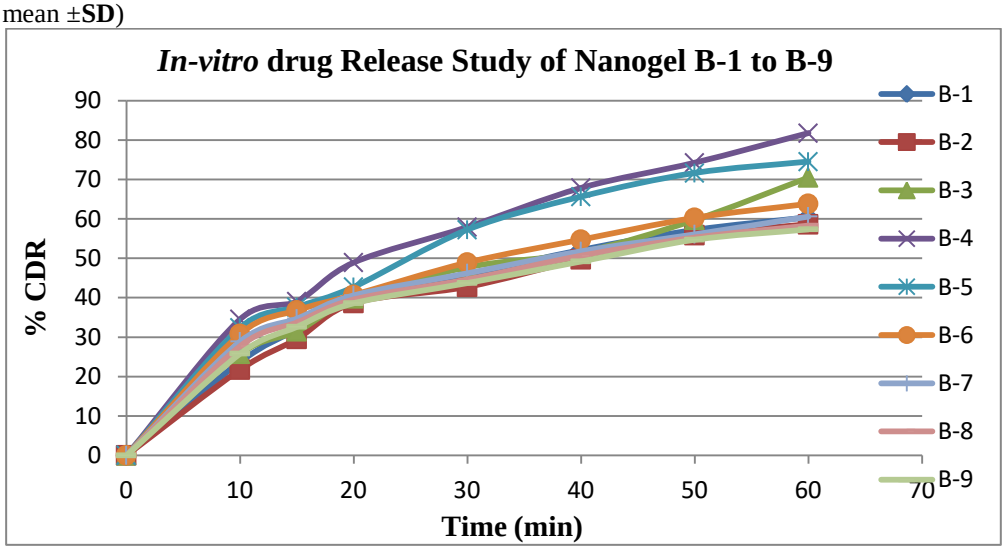

Figure 2: *In-vitro* drug Release Study of Nanogel B-1 to B-9

Biological evaluation of prepared optimized formulations

Table No. 4: Evaluationof anti-inflammation activity using Paw edema volume

Groups	Treatment	Elevated Paw Volume (ml)					
		0 H	0.5 H	1 H	2 H	3H	24 H
Group-I	Control (normal saline)	3.053±0.012*	3.081± 0.031*	3.131± 0.014*	3.017± 0.024*	3.042± 0.028*	3.067± 0.032*
Group-II	Carrageenan	3.026± 0.053	3.125± 0.011	3.462± 0.017	3.541± 0.028	3.868± 0.018	4.277± 0.022
Group-III	Carrageenan + standard drug	3.015± 0.021*	3.274± 0.027*	3.204± 0.018*	3.084±0.015*	3.065± 0.020*	3.116± 0.015*
Group-IV	Carrageenan + pure flurbiprofen	3.029±0.036*	3.124± 0.029*	3.221± 0.011*	3.235± 0.021*	3.284± 0.019*	3.208± 0.013*
Group-V	Carrageenan + nanogel A5	3.017± 0.004*	3.152± 0.031*	3.241± 0.024*	3.163± 0.009*	3.122± 0.033*	3.078± 0.016*
Group-VI	Carrageenan + nanogel B4	3.021± 0.016*	3.133± 0.014*	3.284± 0.020*	3.152± 0.011*	3.130± 0.027*	3.085± 0.012*

Data are expressed as mean ±SEM (n=6 animals),∗Values along columns werestatistically significant at $P<0.05$ when comparedwith Group-II. ANOVA followed by Tukey's test.

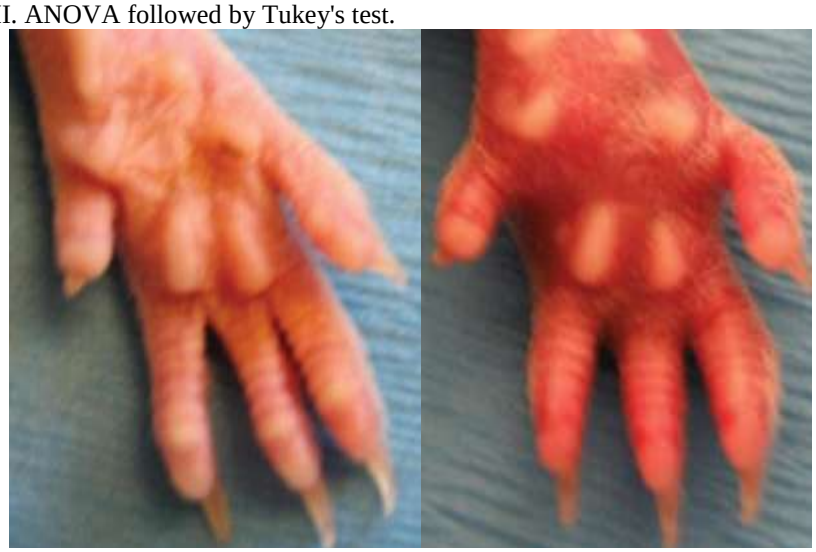

Figure 3: Paw edema after injection of normal saline (left) Carrageenan (right)

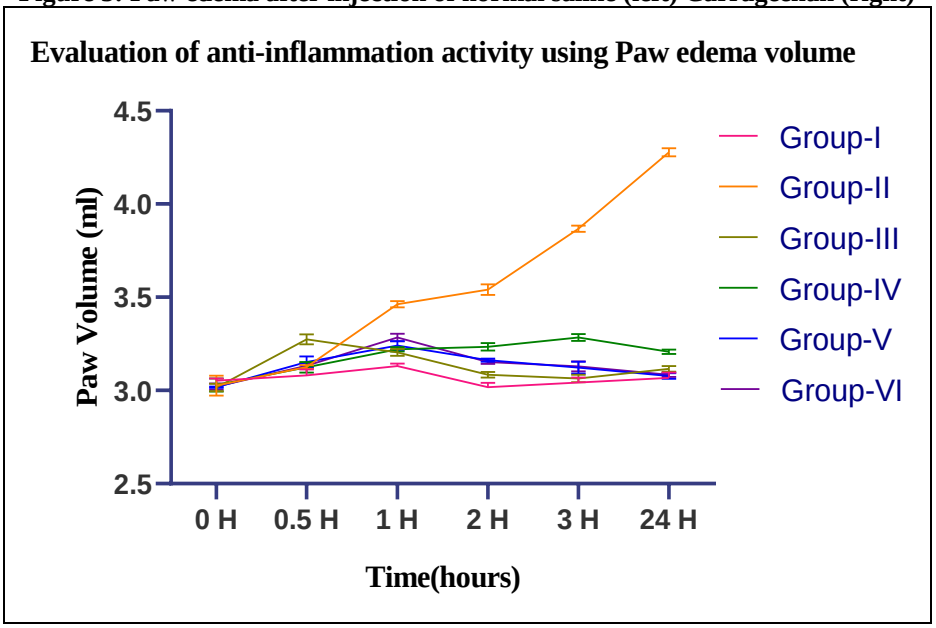

Figure 4: Evaluation of anti-inflammation activity using Paw edema volume

Injection of carrageenan into the hind paw induced a progressive edema reaching its maximum at 3 hours. In case of Group-I animals paw volume found at t = 0 was 3.053 ± 0.012 ml and this remains constant at the end of 24 hours.

Group-II animals had showed an increase in paw volume with each Groups at each hour which was significant at P <0.05. At 0 hours the volume was 3.026 ± 0.053 ml, which increased to 3.868 ± 0.018 ml at t = 3 hours. At 24 hours the thickness was found to be 4.277 ± 0.022 ml. The paw volume of Group-III animals was 3.015 ± 0.021 ml which showed a mild increase at the end of 0.5th hour, that is, 3.274 ± 0.027 ml. After the 0.5th hour it decreased to 3.116 ± 0.015 ml at 24 hours. The paw volume of Group-IV animals showed an increase up to the 24th hour 3.208 ± 0.013 ml volume. The paw volume of Group-V animals was 3.017 ± 0.004 ml which showed a mild increase at the end of 1st hour, that is, 3.241 ± 0.024 ml. After the 1st hour it decreased to 3.078 ± 0.016 ml at 24 hours. The paw volume of Group-VI animals was 3.021 ± 0.016 ml which showed a mild increase at the end of 1st hour, that is, 3.284 ± 0.020 ml. After the 1st hour it decreased to 3.085 ± 0.012 ml at 24 hours. These values were found to be statistically significant at P<0.05.

Table No. 5: Evaluation of anti-inflammation activity using weights of inflamed tissue punch

Groups	Treatment	Weightof tissue punch (mg) after 24 H	*% difference in weight*
Group-I	Control (normal saline)	104.53± 1.21	00.000%
Group-II	Carrageenan	174.67±1.23^{a}	40.156 %
Group-III	Carrageenan + standard drug	107.43± 1.41^{b,}	02.699 %
Group-IV	Carrageenan + pure flurbiprofen	152.65±1.02^{a,b,c}	31.523 %
Group-V	Carrageenan + nanogel A5	121.52±0.97^{a,b,c,d}	13.981 %
Group-VI	Carrageenan + nanogel B4	112.73±0.82^{a,b,c,d,}	07.274 %

Data are expressed as mean ± SEM (n=6 animals), Values along columns werestatistically significant at P<0.05 when compared. ANOVA followed by Tukey's test, where, a (p<0.05 Vs control), b (p<0.05 VsCarrageenan), c (p<0.05 celecoxib), d (p<0.05 Vs flurbiprofen). Carrageenan administration resulted in significant higher weight of tissue punch (174.67 ± 1.23) mg after 24 H, as compare to control group (104.53 ± 1.21) mg. Standard drug celecoxib treated group-III showed significant weight decrease (107.43 ± 1.4) mg as compare to Group-II and inflammation reduced similar to control group. Drug flurbiprofen treated group-IV showed significant weight decrease (152.65 ± 1.02) mg as compare to Group-II, and inflammation reduced but not as the standard drug celecoxib treated Group-III. Nanogel A-5 group-V showed significant weight decrease (121.52 ± 0.97) mg as compare to Group-II, and inflammation reduced but near to the standard drug celecoxib treated Group-III. Nanogel B-4 group-VI showed significant weight decrease (112.73 ± 0.82) mg as compare to Group-II, and inflammation reduced but similar to the standard drug celecoxib treated Group-III. Carrageenan administration resulted in significant higher percentage (%) difference in weight 40.156 % after 24 H, as compare to control Group-I. Percentage (%) difference in weight was observed as the standard drug celecoxib treated group-III have 2.699%, while pure flurbiprofen, nanogel A5 and nanogel B4 has 31.523 %, 13.981 % and 07.274 % respectively. It means higher percentage of inflammation reduced by nanogels other than standard drug.

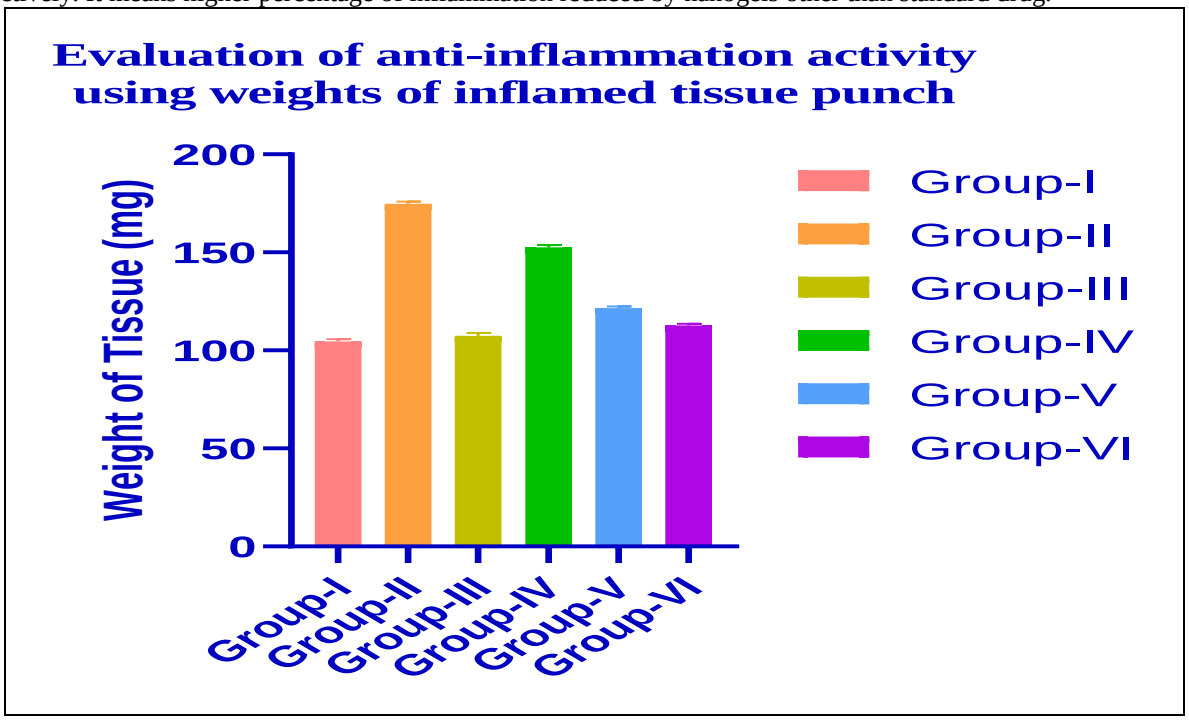

Figure 5: Evaluation of anti-inflammation activity using weights of inflamed tissue punch

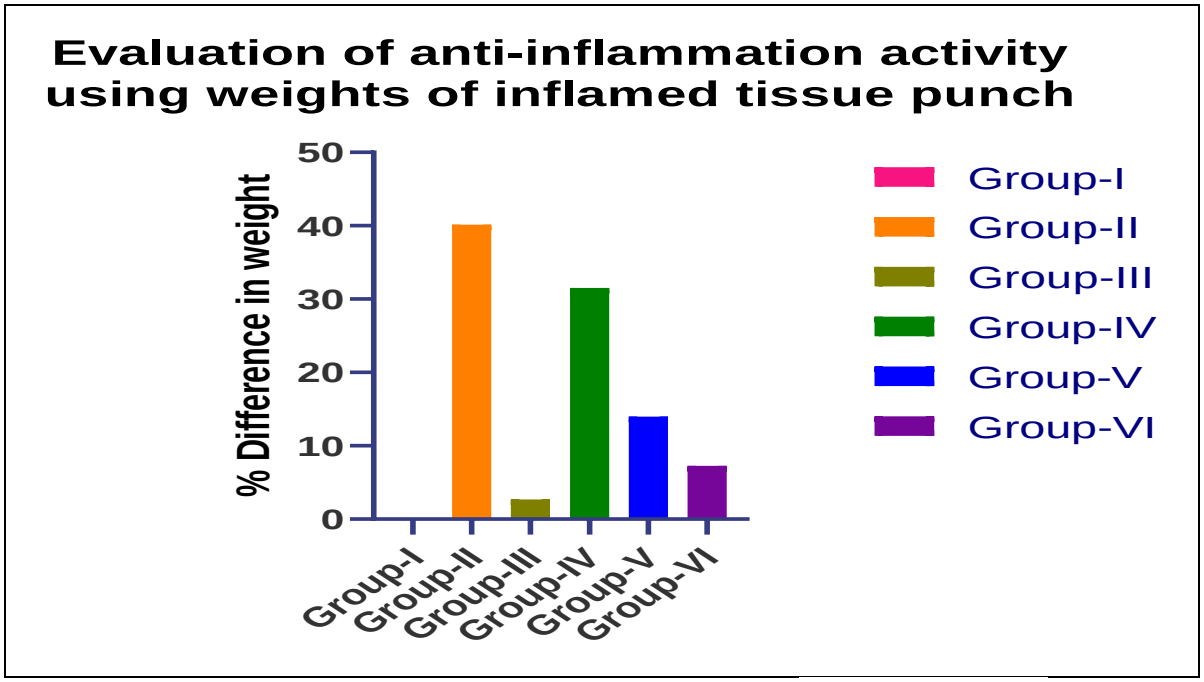

Figure 6: Evaluation of anti-inflammation activity using *% difference in weight*

CONCLUSION

SUMMARY: The drug release from nanogel was determined using through Franz diffusion cell in buffer. The diffusion media of receptor compartment was continuously stirred on magnetic stirrer kept at a temperature of 37 ± 0.5 °C. The amount of drug released from the nanogel was determined by UV spectrophotometer. The result of % cumulative drug release (% CDR) was found highest i.g. 81.74 for B-4. Injection of carrageenan into the hind paw induced a progressive edema reaching its maximum at 3 hours. In case of Group-I animals paw volume found at t = 0 was 3.053 ± 0.012 ml and this remains constant at the end of 24 hours. Group-II animals had showed an increase in paw volume with each Groups at each hour which was significant at P <0.05. At 0 hours the volume was 3.026 ± 0.053 ml, which increased to 3.868 ± 0.018 ml at t = 3 hours. At 24 hours the thickness was found to be 4.277 ± 0.022 ml. The paw volume of Group-III animals was 3.015 ± 0.021 ml which showed a mild increase at the end of 0.5th hour, that is, 3.274 ± 0.027 ml. After the 0.5th hour it decreased to 3.116 ± 0.015 ml at 24 hours. The paw volume of Group-IV animals showed an increase up to the 24th hour 3.208 ± 0.013 ml volume. The paw volume of Group-V animals was 3.017 ± 0.004 ml which showed a mild increase at the end of 1st hour, that is, 3.241 ± 0.024 ml. After the 1st hour it decreased to 3.078 ± 0.016 ml at 24 hours. The paw volume of Group-VI animals was 3.021 ± 0.016 ml which showed a mild increase at the end of 1st hour, that is, 3.284 ± 0.020 ml. After the 1st hour it decreased to 3.085 ± 0.012 ml at 24 hours. These values were found to be statistically significant at P<0.05. Carrageenan administration resulted in significant higher weight of tissue punch (174.67 ± 1.23) mg after 24 H, as compare to control group (104.53 ± 1.21) mg. Standard drug celecoxib treated group-III showed significant weight decrease (107.43 ± 1.4) mg as compare to Group-II and inflammation reduced similar to control group. Drug flurbiprofen treated group-IV showed significant weight decrease (152.65 ± 1.02) mg as compare to Group-II, and inflammation reduced but not as the standard drug celecoxib treated Group-III. Nanogel A-5 group-V showed significant weight decrease (121.52 ± 0.97) mg as compare to Group-II, and inflammation reduced but near to the standard drug celecoxib treated Group-III. Nanogel B-4 group-VI showed significant weight decrease (112.73 ± 0.82) mg as compare to Group-II, and inflammation reduced but similar to the standard drug celecoxib treated Group-III. Carrageenan administration resulted in significant higher percentage (%) difference in weight 40.156 % after 24 H, as compare to control Group-I. Percentage (%) difference in weight was observed as the standard drug celecoxib treated group-III have 2.699%, while pure flurbiprofen, nanogel A5 and nanogel B4 has 31.523 %, 13.981 % and 07.274 % respectively.

CONCLUSION: The present study was aimed to develop Flurbiprofen loaded nanogels for topical drug delivery systems. Thus from above study it can be concluded that the nanogel possessed higher entrapment efficiency. The elicited an increase of the percutaneous permeation of flurbiprofen in-vitro. In addition, In-vitro experiments showed that flurbiprofen Nanogel can ensure a sustained release of the drug and hence a prolongation of its therapeutic activity, which can be related to an

accumulation of flurbiprofen in the skin. These findings are very encouraging and confirm that Nanogels are a very promising carrier for the topical administration due to the enhanced delivery of drugs through the skin thus prompting various opportunities for the development of suitable therapeutic strategies through the topical route. The formulation is easy to scale up as the procedure is simple and do not involve lengthy procedure and unnecessary use of pharmaceutically unacceptable additives.

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