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Development and Evaluation of Flurbiprofen Nanogel Drug Delivery System

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KEYWORDS

Drug, Nanogel, Inflammation, Pain, Redness.

ABSTRACT:

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.

Objectives: The purpose of this study was to develop and evaluate nanogel for transdermal delivery of Flurbiprofen.

Methods: Nanogel was prepared by chemical cross-linked gel method. Nanogel was prepared by the following steps using chemical crosslinked gel method. First, Hyaluronic Acid (HA) (Different concentration like 1% w/v, 2%w/v, 3%w/v) were dissolved in distilled water at room temperature for 1 hr and Polyvinyl alcohol (PVA) (Different concentration like 2.5% w/v, 5%w/v, 7.5%w/v) were dissolved in distilled water at 50OC on magnetic stirrer for 12 hour (1 hour for dissolution and further 11hr for to achieve homogeneous solution).

Results: The Optimization of formulation has been carried out through 32 factorial designs with Hyaluronic acid and polyvinyl alcohol concentration (in percentage W/V) as an independent variables and particle size and percentage drug entrapment efficiency and gelling time as dependent variables.

Conclusions: Nanogels are a very promising carrier for the topical administration due to the enhanced delivery of drugs.

INTRODUCTION:

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]. 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. The five classical signs of inflammationare heat, pain, redness, swelling, and lossof function. 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[2] 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.

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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.

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].

(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].

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.

OBJECTIVES:

The purpose of this study was to develop and evaluate nanogel for transdermal delivery of Flurbiprofen. In recent decades, the skin has become a well-known administration site for topical and systemic drug delivery. Transdermal delivery has a variety of advantages compared with the oral route. Mainly, it is used when the drug shows significant first-pass effect. Further, eliminating the problems associated with de-creased gastrointestinal absorption. Therefore, transdermal administration is beneficial when a constant drug effect is desired. It is therefore desirable to develop a nano formulation system, which does not require the use of penetration enhancers to facilitate drug permeation through the skin. One of the most promising techniques for enhancement of transdermal permeation of drugs is the nanogel techniques.

METHODS:

Method of Formulation of Nanogel: Nanogel was prepared by chemicalcross-linked gel method. Nanogel was prepared by the following steps using chemical crosslinked gel method. The compositions are also recorded in Tables respectively.

Table 1: Preliminary trial for selection of Polymers of Hyaluronic acid and polyvinyl Alcohol

Formulation	Polymer		Crossliker	Catalyst
	Hyaluronic acid (HA) (wt%)	Poly Vinyl alcohol (PVA) (wt%)	Glutaraldehyde (GA) (25%w/v) in mL	Hydrochloric acid (HCl) (6% v/v) in mL
F-1	1	2.5	1	0.2
F-2	1	5	1	0.2
F-3	1	7.5	1	0.2
F-4	2	2.5	1	0.2
F-5	2	5	1	0.2
F-6	2	7.5	1	0.2
F-7	3	2.5	1	0.2

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F-8	3	5	1	0.2
F-9	3	7.5	1	0.2

Table 2: Preliminary trial for selection of Polymers of Hyaluronic acid and Dextran

Formulation	Polymer		Crossliker	Catalyst
	Hyaluronic acid (HA) (wt%)	Dextran (wt%)	Glutaraldehyde (GA) (25%w/v) in mL	Hydrochloric acid (HCl) (6% v/v) in mL
F-10	1	2.5	1	0.2
F-11	1	5	1	0.2
F-12	1	7.5	1	0.2
F-13	2	2.5	1	0.2
F-14	2	5	1	0.2
F-15	2	7.5	1	0.2
F-16	3	2.5	1	0.2
F-17	3	5	1	0.2
F-18	3	7.5	1	0.2

Table 3: Preliminary trial for selection of Polymers of Hyaluronic acid and chitosan

Formulation	Polymer		Crossliker	Catalyst
	Hyaluronic acid (HA) (wt%)	Chitosan (wt%)	Glutaraldehyde (GA) (25%w/v) in mL	Hydrochloric acid (HCl) (6% v/v) in mL
F-19	1	2.5	1	0.2
F-20	1	5	1	0.2
F-21	1	7.5	1	0.2
F-22	2	2.5	1	0.2
F-23	2	5	1	0.2
F-24	2	7.5	1	0.2
F-25	3	2.5	1	0.2
F-26	3	5	1	0.2
F-27	3	7.5	1	0.2

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Optimization of formulation (3^2factorial design) for Flurbiprofen containing nanogel: To optimize the batches, we proceeded by experimental design, which consists in the arrangement of experiments in the design space in such a way that gives reliable and consistent result with minimum number of experiments.

Table 4: Independent variable of Flurbiprofen nanogel

Level	Hyaluronic acid (%W/V)	Polyvinyl alcohol (%W/V)
-1	0.5	2.5
0	1.0	5.0
+1	1.5	7.5

Table 5: Dependent variable of Flurbiprofen nanogel

Dependent Variable	Y1= Particle Size
	Y2= % Drug Entrapment Efficiency
	Y3= Gelling time

Method of Preparation of Flurbiprofen containing nanogel: Flurbiprofen containing nanogel was prepared by chemical cross linked gel method. Flurbiprofen nanogel was prepared by the following steps using chemical crosslinked gel method.

Table 6: The 3^2 factorial design for optimization of Polymer Concentration with Flurbiprofen

Batch No.	HA (%W/V)	PVA (%W/V)	Flurbiprofen(mg)	Glutaraldehyde (25%V/V)	HCl (6% V/V) ml
A-1	0.5	2.5	120	1	0.2
A-2	0.5	5.0	120	1	0.2
A-3	0.5	7.5	120	1	0.2
A-4	1.0	2.5	120	1	0.2
A-5	1.0	5.0	120	1	0.2
A-6	1.0	7.5	120	1	0.2
A-7	1.5	2.5	120	1	0.2
A-8	1.5	5.0	120	1	0.2
A-9	1.5	7.5	120	1	0.2

Table 7: The 3^2 factorial design for optimization of Polymer Concentration with Flurbiprofen

Batch No.	HA (%W/V)	Chitosan (%W/V)	Flurbiprofen(mg)	Glutaraldehyde (25%V/V)	HCl (6% V/V) ml
B-1	1.5	2.5	120	1	0.2

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B-2	1.5	5.0	120	1	0.2
B-3	1.5	7.5	120	1	0.2
B-4	2.0	2.5	120	1	0.2
B-5	2.0	5.0	120	1	0.2
B-6	2.0	7.5	120	1	0.2
B-7	2.5	2.5	120	1	0.2
B-8	2.5	5.0	120	1	0.2
B-9	2.5	7.5	120	1	0.2

6.4 Characterization of Flurbiprofencontaining nanogel:

Appearance of nanogel: The nanogel was checked for its organoleptic properties such as color, odor, clarity, and rheological behavior such as its translucency and homogeneity.

Viscosity measurement: This is an important parameter for the nanogel. Viscosity was measured using Brookfield viscometer employing Spindle (T-shaped spindle) rotated at 5 rpm.

Determination of pH of Flurbiprofen containing nanogel: The pH value was determined using a digital pH meter which was standardized using pH 4 and 7 buffer before use.

Percent drug entrapment efficiency: Around 10 mg drug containing nanogel 1 gm quantity was taken and disperse in 20 ml distilled water, sonicate for 1 hour, filter the dispersion through filter paper (Whatmann Filter Paper Size 0.45 micron) and take Absorbance at UV Spectrophotometer

Free drug measurement: Required quantities of nanogel dispersion were taken and centrifugation at 15,000 rpm for 20 minutes. Above centrifugation process separate free drug at 4°C. Free drug was analyzed using UV spectroscopy in separated supernant.

Entrapped drug measurement: Settled pellets of nanogel were taken and add 10 ml distilled water in beaker, sonicate for 30 minutes, Filtered the dispersion using filter paper (Whatmann Filter Paper Size 0.45 micron), Measure the entrap drug concentration using UV spectroscopy.

$$\textbf{\% Encapsulation Efficiency} = \frac{Total\ drug\ loading - free\ drug}{total\ drug\ loading}\ X\ 100$$

Gelling Time: Nanogel gelling time was measured by using Stopwatch. Adding of Glutaraldehyde as chemical crosslinker in HA-PVA Polymer solution with drop of Hydrochloric acid as catalyst. After addition of glutaraldehyde gelling time was measured for nanogel.

RESULTS

Method of Preparation of flurbiprofen loaded nanogel

Preliminary Trial for selection of Polymers: Preliminary trial for selection of polymers were performed using Hyaluronic acid, Polyvinyl alcohol, Chitosan and dextran as different polymers with different concentration.

Table 8: Preliminary trial for selection of Polymers of Hyaluronic acid and polyvinyl Alcohol

Formulation	Polymer		Crossliker	Catalyst	Observation
	HA (%wt)	PVA (%wt)	GA(25% w/v) in ml	HCl (6% v/v) in ml	
F-1	1	2.5	1	0.2	Optimum gel formulation

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F-2	**1**	**5**	**1**	**0.2**	**Optimum gel formulation**
F-3	**1**	**7.5**	**1**	**0.2**	**Optimum gel formulation**
F-4	2	2.5	1	0.2	Lump formation, thick solution and unstable gel.
F-5	2	5	1	0.2	Lump formation, thick solution and unstable gel.
F-6	2	7.5	1	0.2	Lump formation, thick solution and unstable gel.
F-7	3	2.5	1	0.2	Lump formation, thick solution and unstable gel.
F-8	3	5	1	0.2	Lump formation, thick solution and unstable gel.
F-9	3	7.5	1	0.2	Lump formation, thick solution and unstable gel.

Table 9: Preliminary trial for selection of Polymers of Hyaluronic acid and Dextran

Formulation	Polymer		Crossliker	Catalyst	Observation
	HA (%)wt	Dextran (%)wt	GA (25 % w/v) in ml	HCl (6% v/v) in ml	
F-10	1	2.5	1	0.2	Clear thick solution
F-11	1	5	1	0.2	Clear thicksolution
F-12	1	7.5	1	0.2	Clear thick solution
F-13	2	2.5	1	0.2	Clear thick solution
F-14	2	5	1	0.2	Clear thick solution
F-15	2	7.5	1	0.2	Clear thick solution
F-16	3	2.5	1	0.2	Clear thick solution
F-17	3	5	1	0.2	Clear thick solution
F-18	3	7.5	1	0.2	Clear thick solution

Table 10: Preliminary trial for selection of Polymers of Hyaluronic acid and chitosan

Formulation	Polymer		Crossliker	Catalyst	Observation
	HA (%)wt	Dextran (%)wt	GA (25 % w/v) in ml	HCl (6% v/v) in ml	
F-19	1	2.5	1	0.2	Thick solution, No gel

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F-20	1	5	1	0.2	Thick solution, No gel
F-21	1	7.5	1	0.2	Thick solution, No gel
F-22	**2**	**2.5**	**1**	**0.2**	**Thick gel formed**
F-23	**2**	**5**	**1**	**0.2**	**Thick gel formed**
F-24	**2**	**7.5**	**1**	**0.2**	**Thick gel formed**
F-25	3	2.5	1	0.2	Thick solution, No gel
F-26	3	5	1	0.2	Thick solution, No gel
F-27	3	7.5	1	0.2	Thick solution, No gel

Optimization offlurbiprofenloaded Nanogel (HA-PVA) using 3^2 Factorial Design: The Optimization of formulation has been carried out through 32 factorial designs with Hyaluronic acid and polyvinyl alcohol concentration (in percentage W/V).

Table 11: Optimization of Flurbiprofen loaded Nanogel (HA-PVA) using 3^2 Factorial Design

Batch No.	HA (%W/V)	PVA (%W/V)	Gelling time (min)	Entrapment Efficiency (%)	Particle Size(nm)
A-1	0.5	2.5	7.6 ± 0.43	75.34 ± 0.64	194 ± 0.53
A-2	0.5	5.0	7.4 ± 0.66	77.73 ± 0.43	200 ± 1.43
A-3	0.5	7.5	8.5 ± 0.85	79.42 ± 0.12	211 ± 2.01
A-4	1.0	2.5	7.4 ± 0.33	80.96 ± 0.71	183 ± 3.21
A-5	**1.0**	**5.0**	**5.7 ± 0.78**	**87.34 ± 0.86**	**168 ± 3.04**
A-6	1.0	7.5	6.9 ± 0.33	82.50± 0.34	172 ± 1.02
A-7	1.5	2.5	7.5 ± 0.15	73.47± 0.73	282 ± 1.01
A-8	1.5	5.0	8.9 ± 0.97	64.79 ± 0.16	314 ± 2.43
A-9	1.5	7.5	9.3 ± 0.61	57.47 ± 0.37	342 ± 1.73

(n=3, Mean ±SD)

Characterization of flurbiprofen loaded nanogel (HA-PVA)

Table 12: Appereance of flurbiprofen loaded nanogels (HA-PVA)

Batches	Color	Odor	Clarity	Homogeneity
A-1	Transparent	Slightly Characteristic odor	Clear	Homogeneous
A-2	Transparent	Slightly Characteristic odor	Clear	Homogeneous
A-3	Transparent	Slightly Characteristic odor	Clear	Homogeneous
A-4	Transparent	Slightly Characteristic odor	Clear	Homogeneous
A-5	Transparent	Slightly Characteristic odor	Clear	Homogeneous

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A-6	Transparent	Slightly Characteristic odor	Clear	Homogeneous
A-7	Transparent	Slightly Characteristic odor	Clear	Homogeneous
A-8	Transparent	Slightly Characteristic odor	Clear	Homogeneous
A-9	Transparent	Slightly Characteristic odor	Clear	Homogeneous

Table 13: Characteristic properties of flurbiprofen loaded nanogels (HA-PVA)

S. No.	Batches	Viscosity (cp)	pH	Zeta potential	PDI Mean±SD
1.	A-1	753	**6.8**	-1.81± 0.22	0.241 ± 0.017
2	A-2	688	6.9	-1.73± 0.12	0.211 ± 0.031
3.	A-3	774	7.2	-1.79± 0.01	0.254 ± 0.046
4.	A-4	712	7.4	-1.83± 0.42	0.210 ± 0.072
5.	**A-5**	**702**	**7.1**	**-1.84**± 0.01	**0.231 ± 0.016**
6.	A-6	777	7.3	-1.69± 0.23	0.242 ± 0.029
7.	A-7	738	7.2	-1.81± 0.52	0.258 ± 0.041
8.	A-8	696	7.1	-1.85± 0.23	0.233 ± 0.073
9.	A-9	696	6.8	-1.78± 0.29	0.283 ± 0.054

Optimization offlurbiprofen loadedNanogel (HA-CH) using 3^2 Factorial Design: The Optimization of formulation has been carried out through 3^2 factorial designs with Hyaluronic acid and Chitosan concentration (in percentage W/V).

Table 14: Optimization of flurbiprofen loaded Nanogel (HA-CH)

Batch No.	HA (%W/V)	Chitosan (%W/V)	Gelling time(min)	Entrapment Efficiency (%)	Particle Size(nm)
B-1	1.5	2.5	8.2 ± 0.73	63.43 ± 0.42	321 ±0.53
B-2	1.5	5.0	8.9 ±0.25	67.41 ± 1.53	334 ±1.25
B-3	1.5	7.5	9.0 ± 0.42	68.63 ± 1.42	354 ±1.73
B-4	**2.0**	**2.5**	**7.4± 0.53**	**83.43 ± 0.53**	**293 ± 1.34**
B-5	2.0	5.0	7.9 ± 1.63	79.74 ± 0.16	283 ±0.52
B-6	2.0	7.5	7.7± 1.05	78.53 ± 1.42	263 ±0.62
B-7	2.5	2.5	8.9 ± 0.32	57.34 ± 1.54	267 ±0.73
B-8	2.5	5.0	8.5 ± 1.08	53.41 ± 1.73	254 ±1.12
B-9	2.5	7.5	9.4 ± 0.78	51.61 ± 0.83	231 ±0.82

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Characterization of flurbiprofen loaded nanogel (HA-CH)

Table 15: Appereance of flurbiprofen loaded nanogels (HA-CH)

Batches	Color	Odor	Clarity	Homogeneity
B-1	Transparent, Slightly yellow	Slightly Characteristic	Clear	Homogeneous
B-2	Transparent, Slightly yellow	Slightly Characteristic	Clear	Homogeneous
B-3	Transparent, Slightly yellow	Slightly Characteristic	Clear	Homogeneous
B-4	Transparent, Slightly yellow	Slightly Characteristic	Clear	Homogeneous
B-5	Transparent, Slightly yellow	Slightly Characteristic	Clear	Homogeneous
B-6	Transparent, Slightly yellow	Slightly Characteristic	Clear	Homogeneous
B-7	Transparent, Slightly yellow	Slightly Characteristic	Clear	Homogeneous
B-8	Transparent, Slightly yellow	Slightly Characteristic	Clear	Homogeneous
B-9	Transparent, Slightly yellow	Slightly Characteristic	Clear	Homogeneous

Table No 16: Characterstic properties of flurbiprofen loaded nanogels (HA-CH)

S. No.	Batches	Viscosity (cp)	pH
1.	B-1	923	**6.6**
2	B-2	986	6.6
3.	B-3	952	6.5
4.	**B-4**	**953**	**7.1**
5.	B-5	974	6.8
6.	B-6	952	6.9
7.	B-7	998	7.1
8.	B-8	987	7.0
9.	B-9	978	7.2

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DISCUSSION:

Based on preliminary trials to select polymers, it was concluded that Hyaluronic acid-Polyvinyl alcohol and Hyaluronic acid-Chitosan were observed optimum polymers for further optimization. So, HA-PVA combination within (0.5 to 1.5% w/w HA and 2.5 to 7.5% w/w PVA) and HA-CH combination within (1.5 to 2.5% w/w HA and 2.5 to 7.5% w/w CH) were taken for further optimization. The Optimization of formulation has been carried out through 3^2 factorial designs with Hyaluronic acid and polyvinyl alcohol concentration (in percentage W/V) as an independent variables and percentage drug entrapment efficiency and gelling time as dependent variables. This techniques was effective to indicates the relatively significances of a number of variables and their interactions. Based on optimization using 3^2 factorial designs, it was found that A5 has the maximum drug entrapment. The results shown that the Gelling time was found to be 5.7 ± 0.78 and entrapment efficiency found 87.34% ± 0.86 for A5 batch. The A5 was selected as optimized batch for the further evaluation. Nanogel was checked for its organoleptic properties. Nanogels were transparent, homogeneous, clear and slightly characteristic in odor. Viscosity was measured using Brookfield viscometer employing Spindle (T-shaped spindle) rotated at 5 rpm. Calculated Viscosity was found 702 centipoises for nanogel formulations. Viscosity is main characteristic in preparation of nanogel formulations. Viscosity showed that optimum gel behavior. The pH of each nanogel was determined by using digital pH meter. The pH of nanogel was found to be 7.1. The pH is the main parameter for formulation because in disease condition skin pH varies 6.8 to 7.4. Percent entrapped drug and free drug percentage of nanogel dispersion was determined using the UV spectrophotometric. The entrapment efficiency was found to be increased with increase in polymer content. Batch B5 shows higher drug entrapment efficiency which provides optimum availability of drug at site without any side effects. Nanogel gelling time was measured by using Stopwatch, addition of Glutaraldehyde as chemical cross linker in HA-PVA Polymer solution with drop of Hydrochloric acid as catalyst. After addition of glutaraldehyde, gelling time was measured for nanogel. Gelling time was measured for batch A-5: 5.7 ± 0.78 minutes. Based on optimization using 3^2 factorial design, it was found that B-4 has maximum drug entrapment. The results shown that the Gelling time 7.4 ± 0.53 and entrapment efficiency found 83.43% ± 0.53 for B4 batch. The B4 was selected as optimized batch for the further evaluation. Nanogel gelling time was observed less than other batches.

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