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Preparation and Evaluation of Celecoxib Nanogel

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Shrishail. M. Ghurghure[1], Piyusha V. Das[1]*

D. S.T.S Mandal's College of Pharmacy, Vijapur Road, Jule Solapur Maharashtra. India.

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ABSTRACT

The objective of this work was to prepare celecoxib nanogel for topical delivery, reducing the oral side effects of the drug and enhancing stability. celecoxib is Non-Steroidal Anti-inflammatory agent for the treatment of rheumatoid arthritis. Celecoxib containing topical nanogel prepared by using Carbopol 934 and 940 and characterized for pH, spreadability, drug content, viscosity and *in-vitro* drug diffusion. Among the five formulations, F5 was selected as the best formulation. The pH of all formulations was found near to the skin pH value. The in vitro diffusion study of Fluconazole gel (F5) showed 94.75%. The optimized formulation F5 was checked for the mechanism and kinetics of drug release.

INTRODUCTION:

Nanogels are the polymer based cross-linked hydrogel particles of sub-micrometre size made up of hydrophilic polymers.[1] They are soluble in water, but have properties different from linear macromolecules of similar molecular weight. Such structures along with their bigger analogues. As family of nanoscale particulate materials, hydrogel nanoparticles have been the point of convergence of considerable amount of efforts devoted to the study of these systems dealing with drug delivery approaches. Interestingly hydrogel nanoparticulate materials would demonstrate the features and characteristics of hydrogels and NPs separately possess at the same time.[2] Therefore, it seems that pharmacy world will benefit from both the hydrophilicity, flexibility, versatility, high water absorptivity and biocompatibility of these particles and all the advantages of the nanoparticles, mainly long-life span in circulation and the possibility of being actively or passively targeted to the desired bio phase, e.g. Tumor sites. Different methods have been adopted to prepare nanoparticles of hydrogel consistency. Besides the commonly used synthetic polymers. Active research is focused on the preparation of nanoparticles using naturally occurring hydrophilic polymers. Nanogels are been prepared for the encapsulation of hydrophobic drug so it shows better bioavailability and increases efficacy of the drug. Nanogels act as the carrier-mediated drug delivery system to deliver the drug to the site of action. Nanogels when applied to the skin, even if the gel above gets evaporated from the skin the nanoparticles present gets deep penetrated inside the skin at the site of action and shows the action at the specific site of the skin.[3]

Features of Nanogel: [4]

Size control: Nanogel size and surface properties can be chemically controlled to limit the rate of clearance by phagocytic cells as well as to enable either passive or active cell targeting. Nanogels must be small enough to traverse capillaries and penetrate tissues through either paracellular or transcellular pathways.

Ease of synthesis: The scalability of laboratory-based nanogel development to industrial-scale production for clinical markets and the use of “green” approaches to nanogel manufacturing are important considerations for cost and environmental impact.

High encapsulation stability: Drug molecules loaded into the nanogel need to be retained and not to be transported out or leaked prematurely while circulating in order to provide maximum therapeutic effects and minimum toxicity or side effects.

Controlled and sustained drug release: Drug transport should occur at the target site, thereby providing both therapeutic efficacy and reduced side effects. Drug loading should be sufficiently high to achieve therapeutic goals.

Response to stimuli: Nanogels are designed to respond to specific stimuli must retain high drug encapsulation efficiency stability while circulating to reach target site and drug should release readily to the appropriate stimulus.

- Targeting: Site-specific delivery of nanogels carriers can be achieved via either coupling to their surface affinity ligands binding to target determinants or using responsiveness to local factors as above, or via "passive" targeting approaches including extravasation in the pathological sites and retention in the microvasculature.

- Low toxicity: The nanogels themselves should be highly biocompatible and free from toxicity, and should be biodegradable with non-toxic degradation products that are readily cleared from the body.

MATERIALS AND METHODS:

Materials:

Carbopol 934, Propylene glycol, Glycerin, Triethanolamine and celecoxib

Method of preparation:

Celecoxib nanoparticles were prepared by antisolvent precipitation method. The gel is been prepared by dispersion method by dispersing Carbopol 934 in water for 2 hours for swelling. Once the Carbopol has been swelled it is been kept on magnetic stirrer for the stirring and prescribed amount of nanoparticles is been added in the Carbopol mixture, along with the propylene glycol which acts as the penetration enhancer and glycerin which acts as a humectant and viscosity modifier is been added into the mixture. pH is been maintained using triethanolamine.

EVALUATION OF GEL:

Percentage yield:

The empty container was weighed in which the gel formulation to be stored and again the container was weighed with gel formulation. Subtract the empty weight of the container with

the weight of container with gel formulation. The difference in weight was considered as the practical yield. The percentage yield was calculated by using;

Measurement of pH:

The pH of gel formulation is determined by a digital pH meter.1 g of gel is dissolved in 100 ml distilled water and stored for two hours. The measurement of the pH of each formulation is done in triplicate and average values are calculated.

Drug content studies:

Accurately weighed 1 g of gel was transferred into 10 ml volumetric flask containing 5 ml of ethanol and stirred for 30 min followed by sonication. The volume was made up to 10 ml with ethanol. 5 ml of the above solution was further diluted to 10ml with ethanol. The absorbance was measured using UV Visible spectrophotometer at 254 nm.

Spreadability:

The Spreadability of all formulations was determined by using the horizontal plate method. 1 g of gel was placed between two horizontal glass plates and standard weight (125 g) was tied on the upper glass plate. The whole set was held in the vertical position. The time was noted for the plate to slide off from the other plate. The spreadability was calculated from the following formula,

$$S = (m \times l) / t$$

Where 'S' is the spreadability coefficient, 'm' is the weight tied to the upper slide, 'l' the length of glass slide and 't' is the time taken.

Viscosity measurement:

The viscosity of the gel was determined by using Brookfield viscometer. Accurately weighed 25 gm of celecoxib gel was transferred to 50 ml glass beaker. Spindle no 6 was selected and it is immersed into the gel. The viscometer was operated at 10 rpm until the reading gets stabilized and reading was noted in centipoises. It was noted from the literature that the formulations after gelling should have a viscosity of 50 –50,000 cps.

In-vitro diffusion studies:

In-vitro diffusion study was carried out in a Franz diffusion cell using cellophane membrane which is soaked overnight in distilled water. The membrane was tied to the donor compartment and mounted on the reservoir compartment of Franz diffusion cell containing 150 ml of pH 7.4 phosphate buffer. 1 gm of celecoxib gel was placed over the cellophane membrane of donor compartment. Whole set was placed on the magnetic stirrer. The study was carried out at 37±0.5 ºC and 100 rpm for 12 h. Samples were withdrawn from the sampling port of the reservoir compartment at regular intervals and absorbance was measured using UV visible spectrophotometer at 261 nm.

The % Drug release from the Celecoxib nanogel at different time intervals were fitted to zero order kinetics and first-order kinetics model, Higuchi model and Korsemeyer Pappas model to characterize the mechanism of drug release. To characterize the release mechanism, the diffusion data are evaluated.

RESULTS AND DISCUSSION:

Table 1: Absorbance of Celecoxib at different concentrations in ethanols

Sr. No.	Concentration (µg/ml)	absorbance
1	0	0
2	0.2	0.129
3	0.4	0.228
4	0.6	0.331
5	0.8	0.421
6	1	0.531

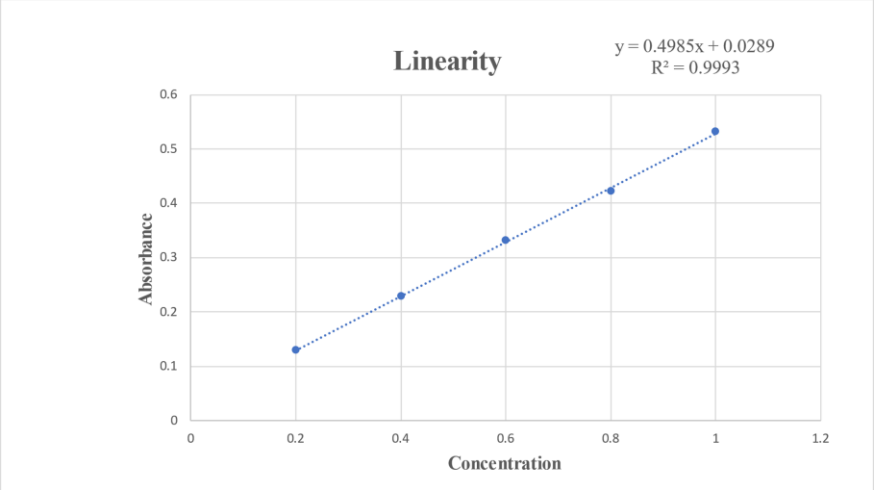

Fig 1: Calibration curve of Celecoxib in ethanol

FTIR Characteristics Peaks of Pure Celecoxib Drug:

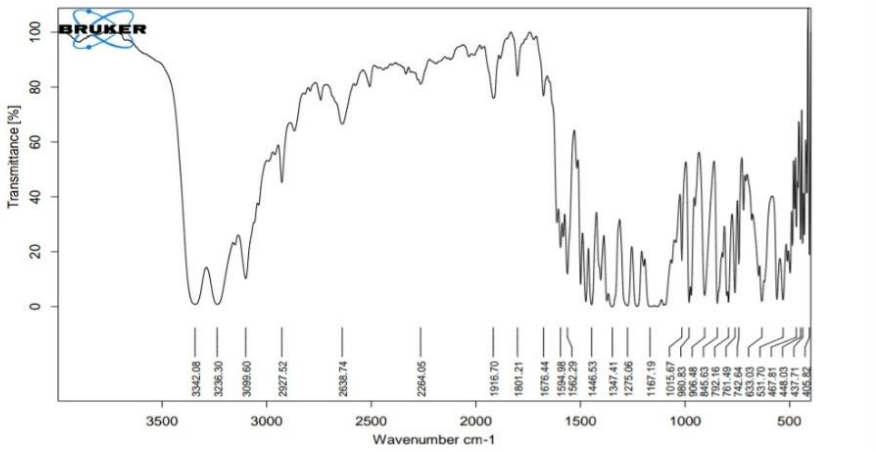

Fig 2: IR spectrum of Celecoxib drug

Table 2: IR interpretation of Celecoxib drug

Frequency cm^{-1}	**bond**	**Functional group**
3500-3200(s)	O-H stretch, H-bonded	Alcohols
1360-1290(m)	N-O symmetric stretch	Nitro compounds
1300-1150(m)	C-H wag	Alkyl halides
3500-3200(s)	O-H stretch	H-bonded alcohols

Evaluation of Celecoxib nanogel:

Table 3: Evaluation of Celecoxib nanogel:

Formulation code	Percentage yield (%)	Drug content (%)	pH	Spreadability (gm.cm/sec)	Viscosity (cps)
F1	91.5	89.9±0.900	6.8	11.0	6900
F2	90.2	90.31±0.412	7.1	11.1	8300
F3	90	93.0±0.996	6.8	10.8	7115
F4	89	91.11±0.339	6.9	11.7	9200
F5	91.6	95.0±1.145	6.7	11.1	9200

Table 4: Table3: *In-vitro* diffusion release of Celecoxib nanogel (G5):

Time (h)	G1	G2	G3	G4	G5
0	0	0	0	0	0
1	13.65±0.015	16.42±0.763	14.66±0.712	13.42±0.669	30.54±0.824
2	28.96±1.24	32.07±0.489	30.69±0.834	30.71±0.445	42.32±0.511
4	39.89±1.35	40.54±2.322	40.5±1.232	40.37±0.473	55.70±1.011
6	47.71±2.205	55.3±1.018	56.4±1.240	52.04±0.714	65.85±0.251
8	56.7±1.103	61.7±1.705	62.10±0.313	59.4±0.282	77.92±1.411
10	64.53±0.221	70.8±0.706	69.9±0.386	66.21±0.190	86.26±0.339
12	70.61±1.269	77.9±1.411	74.81±0.493	71.71±0.200	94.75±0.703

***In-vitro* diffusion release of Celecoxib nanogel:**

In-vitro drug release of the 5 formulations was carried out using Franz diffusion cell. The amount of the drug released after 12 hours was in the range of 70.61 to 94.75% respectively.

The formulation G5 showed better-sustaining effect amongst all the formulations in the range of 94.75%.

CONCLUSION:

In the present study, an attempt was made to formulate celecoxib nanogel for efficient delivery of drug to skin. Celecoxib shows maximum absorption at a wavelength of 254nm in ethanol. The value of the correlation coefficient was found to be R^2=0.9993, which showed linear relationship between concentration and absorbance. Thus, it can be concluded that, beer's law was obeyed.

Nanogel was prepared and subjected to physicochemical studies and in vitro release studies. The pH of all formulations was in the range of 6.8 to 7.21 which lies in the normal pH range of the skin. The spreading area was found to decrease with an increase in viscosity. From the in-vitro drug release results it was found that, G5 shows highest drug release rate. The objective of the present work of development and evaluation of nanogel containing anti-inflammatory celecoxib drug has been achieved with success.

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