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THE DEVELOPMENT AND EVALUTIONOF NANOSPONGES DRUG DELIVERY SYSTEM OF KETOPROFIN BY USING SOLVENT EVAPORATION METHOD.

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ABSTRACT

The Aim ofthisworkistothedevelopmentandevaluationof Nanosponges drug delivery system of Ketoprofen by using solvent evaporation method.Ketoprofen is a BCS classII drug, having anhalf life of 1.1-4 hours, which wasn't suitable for maintaining constant plasma concentrations. So Ketoprofen was formulated as a Nanosponge formulation for effective drug release. KetoprofenNanosponges was formulated using poloxamer, ethyl cellulose, β-cyclodextrin with four different drug: polymer rations. FTIR spectroscopy analyses indicated the chemically stable, amorphous nature of the drug in these Nanosponge. SEM photographs revealed the spherical nature of the Nanosponge in all variations. The formulation F8 has better results than remaining formulations. F8 formulation shows better entrapment efficiency than other formulations, drug release release96.42 % in 12 hour, and follows zero order with supercase II transport mechanism.

Keywords: Ketoprofen, Ethyl cellulose, Poloxamer, β-cyclodextrin, FTIR.

INTRODUCTION

In recent years, there has been considerable emphasis given to the development of novel nanosponge base drug delivery systems, in order to modify and control the release behavior of the drugs. By incorporation into a carrier system, it is possible to alter the therapeutic index and duration of the activity of drugs. [1]The ever-increasing interest among consumers with regard to skin care and skin treatment products has been fostered by the widespread use of ingredients like α-hydroxy acids and vitamins in topical products, which can induce perceivable and demonstrable benefits – especially in aging or photo-damaged skin. Although quite useful, in many instances, these ingredients may produce irritancy; such irritancy can be perceived as burning, stinging or redness and particularly occurs in individuals with sensitive skin. Recognizing this problem, the formulators have attempted to deal with this problem in one of the two methods.[2] Nanosponges are novel class of hyper-crosslinked polymer based colloidal structures consisting of solid nanoparticles with colloidal sizes and nanosized cavities. They enhance stability, reduce side effects and modify drug release. The outer surface is typically porous, allowing sustain release of drug. They are mostly use for topical drug delivery. Size range of nanosponge is 50nm-100nm[1,3]They can be used for targeting drugs to specific sites, prevent drug and protein degradation. These tiny sponges can circulate around the body until they encounter the specific target site and stick on the surface and began to release the drug in a controlled and predictable manner. It is possible to control the size of nanosponge. To varying the portion of cross-linkers and polymers, the nanosponge particles can be made larger or smaller[4].A Nanosponge Delivery System (MDS) is patented,

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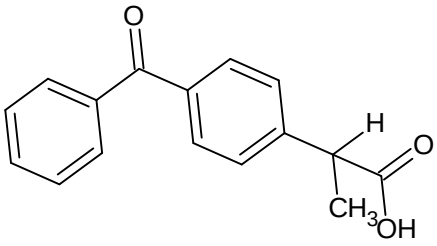
highly cross-linked, porous, polymeric microspheres that can entrap wide range of actives and then release them onto the skin over a time and in response to trigger. This system was employed for the improvement of performance of topically applied drugs.[5]Ketoprofen is a BCS class II drug, having anhalf-lifeof 1.1-4 hours, which wasn't suitable for maintaining constant plasma concentrations. So Ketoprofen was formulated as a nanosponge formulation for effective drug release.[6]Ketoprofen is a non-steroidal anti-inflammatory drug with analgesic and antipyreticproperties. During inflammation, pain and fever, arachidonic acid isliberatedfromphospholipidfractionofthecellmembrane;arachidonicacidis then convertedviacyclo-oxygenase (COX-1 and 2) pathways to prostaglandins (PGs), bradykinins,leukotrienesetc.



2-(4-benzoylphenyl)propanoic acid

METHODOLOGY

- Prior to the development of nanosponge dosage form, it is essential that certain fundamental physical and chemical properties of the drug molecule alone and when combined with excipients are determined.[7]To evaluate the drug substance analytically and determine its necessary characteristics, and To establish its compatibility with different excipients.[8]

Solubility studies:

Solubility of Ketoprofen was carried out in different solvents like- 0.1N HCL, 7.4pH buffer and 6.8 pH buffer, and also in organic solvents like Ethanol, Methanol. Solubilitystudieswere performedbytaking excessamountofdrug indifferent beakerscontainingthesolvents[9]. Themixtureswereshakenfor24hrs atregular intervals.Thesolutionswerefiltered by usingwhattmann'sfilterpapergradeno.41. The filtered solutions were analyzed spectrophotometrically.[10]

Method of Preparation of Nanosponges by solvent Evaporation method:

Nanospongesusing different proportionsofβ-cyclodextrin, ethyl cellulose, poloxamer as rate retarding polymer and co-polymers like polyvinyl alcohol werepreparedbysolventevaporationmethod.[11] Dispersephaseconsisting ofKetoprofenand requisitequantity ofPVA dissolved in 20 ml solvent (Methanol) wasslowly added toadefiniteamountofPVA in40mlofaqueouscontinuousphase,prepared by usingmagnetic stirrer.Thereactionmixturewas stirred at1000RPM on a magnetic stirrer for 2hours and kept on hot plate upto complete removal of organic solvent from the formulation.The Nanospongesformedwerecollectedby filtrationthroughwhatmanfilter paperanddried.[12]

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LIST OF EXCIPIENTS AND EQUIPMENTS

TABLE 1.1: Excipients Used In Design of Formulation

Excipient Used	**Supplier**
Ketoprofen	XENON PHARMA PVT LTD
β-Cyclodextrin	Lobachemie, Mumbai
Polyvinyl alcohol (PVA)	Lobachemie, Mumbai
Poloxamer	Lobachemie, Mumbai
Ethyl Cellulose	Lobachemie, Mumbai
Methanol	Narmada chemicals
Water	Narmada chemicals

Table 1:1: Formulation table of Ketoprofen loaded Nanosponges using solvent evaporation method

Excipients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
Ketoprofen (g)	1	1	1	1	1	1	1	1	1	1	1	1
β-cyclodextrin (g)	1	2	3	4	--	--	--	--	--	--	--	--
Ethyl Cellulose (g)	--	--	--	--	1	2	3	4	--	--	--	--
Poloxamer (g)	--	--	--	--	--	--	--	--	1	2	3	4
PVA (mg)	500	500	500	500	500	500	500	500	500	500	500	500
Methanol	20	20	20	20	20	20	20	20	20	20	20	20
Water (mL)	40	40	40	40	40	40	40	40	40	40	40	40

Equipments Used In Design Formulation:

SNo.	**Instruments**	**Sources**
1	Electronic Weighing Balance	Shimadzu Corporation Tokyo, Japan
2	UV-Vis Spectrophotometer (T60)	PG Instrument
3	FTIR Spectrophotometer	Shimadzu Corporation Tokyo, Japan
4	Dissolution Apparatus	LAB India
5	Magnetic stirrer	Remi industries, Kerala

Evaluationparameters of Nanosponges :

Particle size measurement

The particle size was determined using the particle size analyzer (Zeta sizer Nano series, UK). The formulations were diluted with an appropriate volume of phosphate buffer solution (PBS, pH 6.8)[13]. The measurements were carried out three times where the mean value was used.

Dissolution study:

Dissolution Parameters

Medium : 900ml, 0.1N HCL for 2hrs and 6.8pH buffer for 10hrs.

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Apparatus : Basket (USP-I)
RPM : 50
Temperature : 37º C±0.5
Time Points : 1, 2, 3,4,5,6,7,8,9,10,11,12 hr
Procedure:

For the oral dosage forms the in vitro dissolution study must be conducted in the dissolution medium which simulate the in-vivo conditions (actual physiological conditions).[14] The in vitro drug release studies for the prepared formulation were conducted for a period of 12 hrs using an Electro lab model dissolution tester USP Type-1 apparatus (rotating basket) set at 50 RPM and a temperature of 37± 0.5°C weight equivalent to 50mg of Ketoprofennanosponge was filled in capsule and kept in basket apparatus and placed in the 900ml of the medium. At specified intervals 5ml samples were withdrawn from the dissolution medium and replaced with fresh medium to keep the volume constant[15].The absorbance of the sample solution was analyzed at 261 nm for the presence of model drug, using a UV-visible spectrophotometer.

Entrapment efficiency

The200mgofthe Ketoprofen weight equivalentnanosponge wasanalyzedbydissolvingthesamplein 10mlofmethanol.Afterthedrugwasdissolved 10ml ofclearlayerofdissolveddrugis taken. Thereaftertheamountofdrug inthewaterphasewas detectedbyaUV-Spectrophotometricmethodat246 nm(U.V Spectrophotometer). Theconcentrationofthedrug isdetermined with thehelpof calibration curve[16].The amount of druginsidetheparticleswascalculatedby subtracting theamountofdrug intheaqueousphasefromthetotalamountofthe drug inthe Nanosponges.The entrapmentefficiency (%) ofdrugwas calculated bythe following equation.[17]

$$\%\text{ofDrugentrapment} = \frac{\text{Massofdruginnanosponge}}{\text{Massofdrugusedinformulation}} \times 100$$

Scanning electron microscopy

The morphological features of prepared Nanosponges are observed by scanning electron microscopy at different magnifications.

Table No: Drug transport mechanisms suggested based on 'n' value.

S. No	Release exponent	Drug transport mechanism	Rate as a function of time
1	0.5	Fickian diffusion	$t^{-0.5}$
2	0.45 < n = 0.89	Non -Fickian transport	t^{n-1}
3	0.89	Case II transport	Zero order release
4	Higher than 0.89	Super case II transport	t^{n-1}

The exponent of n the portion of the release curve, where Mt / M∞ < 0.6 should only be used. To study the release kinetics, data obtained from in vitro drug release studies were plotted as log cumulative percentage drug release versus log time.[18]

RESULTS & DISCUSSION

Solubility Studies of Ketoprofen

Buffer	**Solubility (mg/ml)**
0.1 N HCL	0.549
6.8 pH buffer	0.896
7.4pH buffer	0.658
Ethanol	2.986

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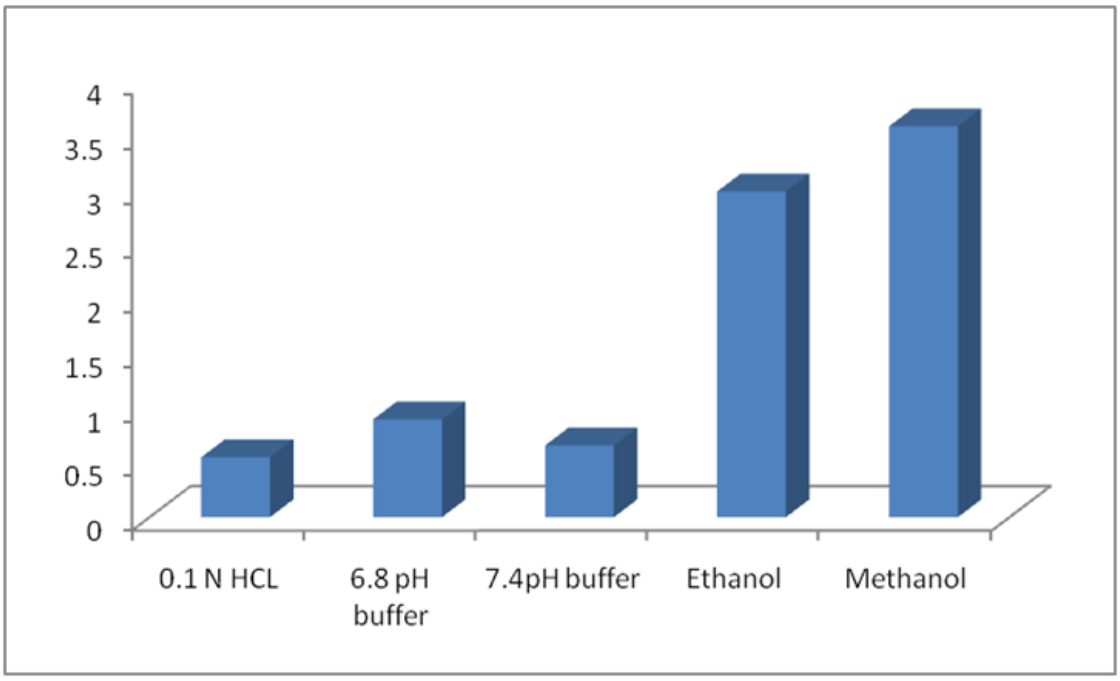


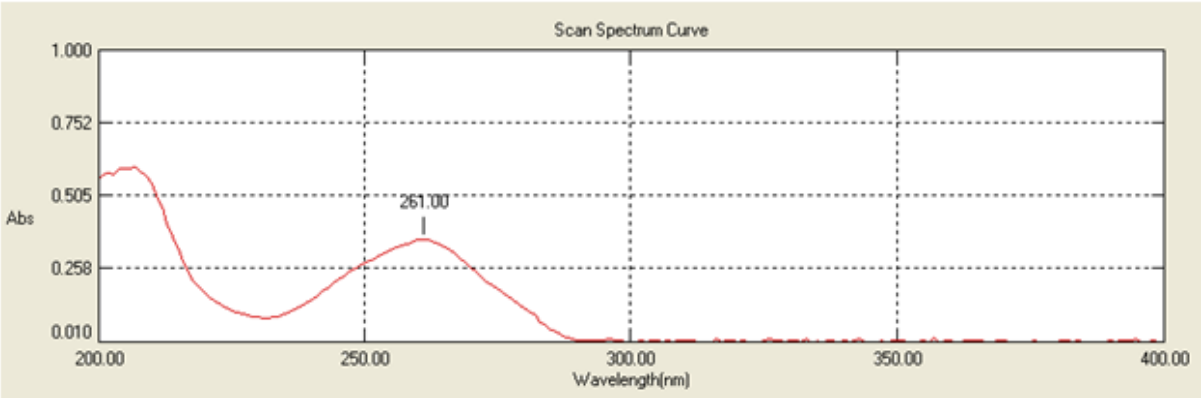
Solubility Studies of Ketoprofen

Discussion: From the above obtained solubility studies we can say solubility of the drug is more in 6.8pH buffer than the other buffers. In organic solvents the solubility was found more in methanol.[19]

Determination of melting point

The melting point of Ketoprofen was found to be 116° C which was determined by capillary method. [20]

Determination of absorption maximum (λmax): Determination of Ketoprofen λ-max was done in 6.8 pH phosphate buffer for accurate quantitative assessment of drug dissolution rate. 21



λ-max in 6.8 phosphate buffer

Discussion: The maximum absorbance of the Ketoprofen in pH 6.8 buffer was found to be 261nm.

Calibration curve:

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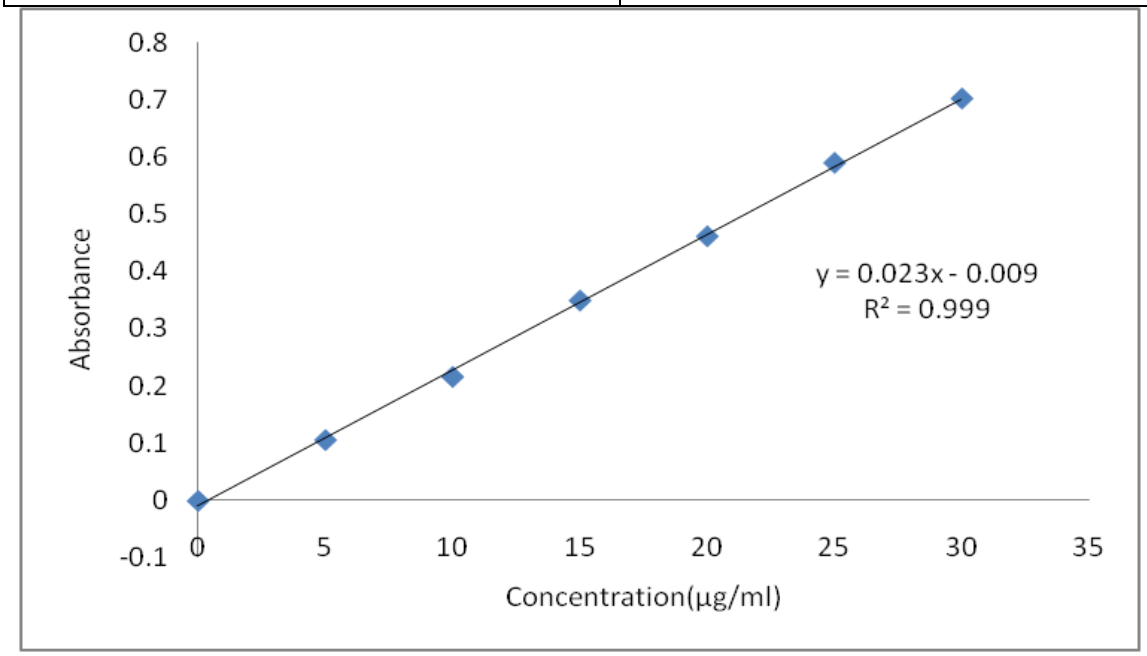
Table 6.2: Calibration curve data ofKetoprofen in 0.1N HCL:

Concentration (µg/mL)	Absorbance
0	0
5	0.106
10	0.216
15	0.349
20	0.461
25	0.589
30	0.701



Calibration curve data of Ketoprofen in 0.1N HCL

Table 6.3: Calibration curve of Ketoprofen in 6.8 pH buffer:

Concentration (µg/mL)	Absorbance
0	0
5	0.138
10	0.262
15	0.392
20	0.508
25	0.659
30	0.768

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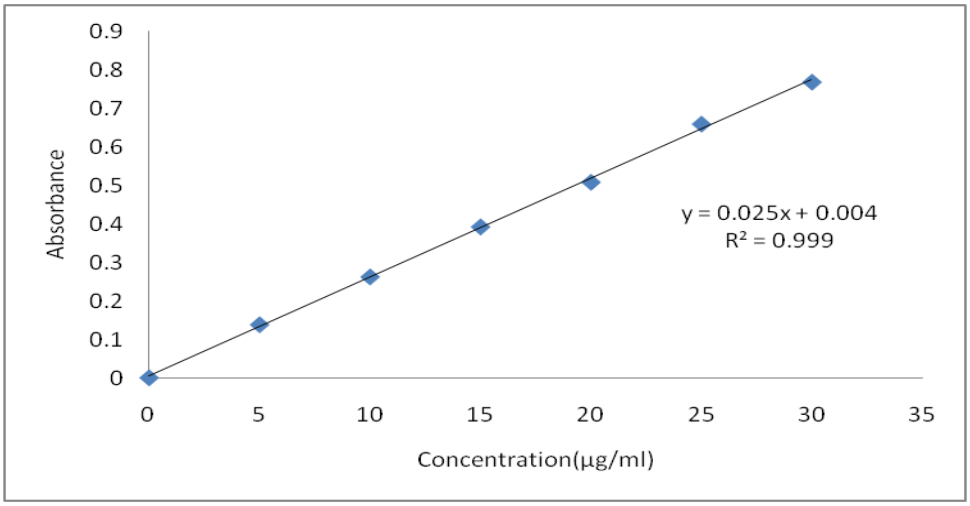

Calibration curve of Ketoprofen in 6.8 pH buffer

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CONFLICTS OF INTEREST
Author declares that there have been no conflicts of interest.

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