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APPLICATION OF NANOGEL AS A TOPICAL DRUG DELIVERY VEHICLE FOR DICLOFENAC SODIUM

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Abstract

Diclofenac is an analgesic and belongs to the non steroidal and anti inflammatory drug [NSAIDS] that is widely used to tricot pain and inflammation. When used by the oral route, only about 50% of absorbed dose of diclofenac becomes systematically available due to first-pass metabolism. The objectives of the present investigation were the product quality and performance must be comparable to the innovator product in the order to ensure therapeutical equivalence. The present study is to formulate nanosize dispersion of diclofenac sodium by emulsion solvent diffusion method and incorporation of gelling agent to product nanogel. The formulation and characterized for particle size range from 100-400 nanometers. A drug name diclofenac sodium used in chronic diseases. FTIR spectrum it was concluded that the drug sample was in pure form. It was found that drug absorbance is 226 & 276 nm but maximum absorbance was at 276nm. When solution is prepared in distilled water for quantitative evaluation purpose through the medium of evaluation of release in phosphate buffer PH 6.8. The graph absorbance Vs concentration was found to be linear in the concentration range of 424µg/ml at 276nm. The R2 of the calibration curve was found to be 0.999. Nanogel formation containing diclofenac sodium was successfully prepared and shows effective as was as better carrier for the topical preparation. The production of formulation also proceeds be better and cost effective comparision with oral dosage forms.

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Introduction

Diclofenac is a pain reliever and belongs to the class of Nonsteroidal anti-inflammatory drugs (NSAIDs), which are widely used to treat pain and inflammation. It works by blocking the production of prostaglandins, which cause inflammation. However, the use of diclofenac has been associated with several side effects, including Nephrotoxicity. Nephrotoxicity is a major concern because it can lead to kidney failure. The exact mechanism of diclofenac-induced nephrotoxicity is not fully understood. However, it is thought to be mediated by inflammation, oxidative stress, and depletion of renal antioxidant molecules such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). Oxidative stress is a condition in which there is an imbalance between the production of free radicals and the body's ability to neutralize them. Free radicals are unstable molecules that can damage cells and tissues. Diclofenac-related kidney damage has also been associated with inflammation, a complex biological process characterized by the release of inflammatory cytokines that play an important role in the immune response. Tumor necrosis factor alpha and interleukin-1β (TNF-α and IL-1β) are involved in the recruitment of inflammatory cells to the site of infection or injury. They also promote the release of other pro-inflammatory cytokines. The aim of this study was to investigate the effects of diclofenac on renal antioxidants and cytokines in male Wistar rats. After oral administration, only about 50% of the absorbed dose of diclofenac becomes systemically available due to first-pass metabolism. In addition, oral diclofenac can cause significant side effects, especially those related to the gastrointestinal tract, due to high plasma concentrations. Transdermal patches have recently been developed as innovative local delivery systems for diclofenac and other anti-inflammatory drugs. They have the advantage of continuous drug delivery and a lower incidence of systemic side effects due to lower plasma concentrations. Medications commonly used to treat inflammation include nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, ketoprofen, (S)-

naproxen, nimesulide, meloxicam, and celecoxib, certain plant polyphenols such as quercetin, curcumin, and chrysophanol, and certain polyphenols. resulting alkaloids such as capsaicin and piperine. Also, when developing generic products, the quality and performance of the product must be comparable to the innovative product to ensure therapeutic equivalence. Most drugs used topically at the site of action require clinical BE outcome studies, including non-steroidal anti-inflammatory drugs (NSAIDs) such as diclofenac sodium. When applied topically, diclofenac inhibits the formation of prostaglandins and can be useful in the treatment of acute and chronic pain. More than 50% of synthetic and plant-derived agents/compounds for both acute and chronic inflammation are poorly soluble in water, limiting their use. In comparison, emulsion-based formulations are best suited to overcome problems related to poor solubility and bioavailability. The use of nanoemulsions (NEs), currently used in established drug delivery systems, is a promising alternative delivery strategy for lipophilic drugs and can improve both their permeability and bioavailability by improving local absorption. Emulsion-based formulations are best suited to address poor solubilities and bioavailabilities. The use of nanoemulsions (NE), currently used in established drug delivery systems, is a promising alternative delivery strategy for lipophilic drugs and can improve both their permeability and bioavailability by improving local absorption. Comparison of nano emulsion-based gel formulation (F1 NE).)), was performed to evaluate their effectiveness solid dispersion-based gel and the commercially available product Nystatinb® cream for evaluation. An optimized formulation was selected for further study. The antifungal effect of the optimized formulation of Nystatin gel was evaluated and compared with Nystatin® cream in patients with cutaneous candidiasis. The objective of this story is used to investigate the effect of some penetration enhancers on the release of Diclofenac sodium as a mode of water soluble drug from polymeric films &its permeation through abdominal rat skin & also to study Physicochemical and Physiochemical character of the prepared Nanogel,polymer, penetration enhancers in different concentrations.To developed a Nano gel with reduced particle size in order to improve the bio availability of the anti inflammatory drugs (diclofenac sodium).To develop diclofenac sodium nanogel for managing pain and inflammation using the low energy emulsification technique.. To design or evaluate diclofenac sodium nanogel which provides prolonged release. To investigated the increase the residence time or drug on the skin thereby enhance bio availability and bio degradability. The objective of the present investigation is to formulate, optimize and characterise nano emulsion gel containing diclofenac sodium formulation for topical delivery.

Materials and Methods

Table no 1.0: Materials used for the formulation development

Sl. no	Materials	Manufacture company
1	Diclofenac sodium	CIPALA PVT .LTD
2	Eudragit –S100	CIPALA PVT .LTD
3	Glycerol	CIPALA PVT.LTD
4	Carbopol	CIPALA PVT.LTD
5	Tween-80	CIPALA PVT .LTD
6	Triethanolamine	CIPALA PVT.LTD

Table no 1.2: List of equipments used

Sl.no	Name of the equipments
1	Autoclave
2	Magnetic stirrer
3	Rotary evaporator
4	Homozinizer
5	PH meter
6	Microscope
7	Ultra sonic bath (sonicator)
8	Dessicator
9	Refrigerator

Rational for drug selection

Diclofenac inhibits cyclo oxygenease -1 & 2 the enzymes responsible for production of prostaglandin (PG) G2 Which is the precursor to other PGs . These molecules have broad activity in pain and inflammation and the inhibition of their production is the common mechanism linking each effect of diclofenac.

It mediates peripheral sensitization through a variety of effects. PGE2 activates the G-coupled EP1 receptor leading increased activity of inositol triphosphate by phospholipase C51 pathway presynaptically, this receptor is increased the release of neurotransmitter glutamate, CGRP, And substance Post synaptically it increases the activity of AMPA and NMDA receptors and produce inhibition of inhibitory glycinergic neurons.

Rational for selection of excipients

Compatability studies

The selection of excipient was based on prior experience: Excipients listed by the innovator in the formulation of nanogel. And the observed compatability of the excipients with diclofenac sodium.

1. Eudragit S-100: Eudragit S-100 are anionic copolymer based on methacrylic acid and methyl methacryclate .
2. Glycerol: Glycerol is under the category of poly hydric alcohol due to its chemical structure: the prescence of 3hydroxy groups within a glycerol molecule.
3. Carbopol: Carbopol polymer is a white powder cross linked polyacrylic acid polymer. It is extremely efficient rheology modifier capable of providing high viscosity and forms sparkling clear gels are hydro alcoholic gels and creams.
4. Tween-80: Tween -80 is a non ionic surfactant and emulsifier this synthetic compounds a viscous , water soluble yellow liquid it is derived from polyethoxylated sorbitol and oiscous lileic acid .

5. Triethanolamine: It is a organic compound with the chemical formula N (CH2CH2OH) O3 it is a colourless, viscous liquid .It is both a tertiary amines and a triol.

Preformulation Studies

Preformulation testing was an investigated of physical and chemical properties of a drug substances alone and when combined with excipients. The use of preformulation parameters maximizes the chance in formulating an acceptable, safe efficacious and stable products. Preformulations study were carried out to serve following purpose

1. To finilalize specifications of active pharmaceutical ingredients.
2. To study the compatability between active and inactive ingredients.
3. Characterization of reference product.
4. Preformulation study can be divided into two sub classes:
    1. API characterization
    2. Compatability study

Active pharmaceutical ingredient (API) Characterization:

Organoleptic characterization: These are preliminary characterstic of any substance which is usefull in identifaction of specific material.

Following physical properties of API were studied

Table no 1.3: Organoleptic and solubility analysis of diclofenac sodium:

Parameter	Diclofenac sodium
Appearance	Odourless, white to off-white crtstalline, slight hygroscopic powder.
Solubility analysis	It is soluble in water, ethanol ,methanol, acetone.

Loss on Drying

1.0g of diclofenac sodium was accurately weighed and the powder was kept in a moisture balance apparatus for 3mins. At 105 degree centigrate and the moisture content was calculated.

Bulk Density

Bulk density was determined by pouring gently 20g of sample (diclofenac sodium) through a glass funnel into 50ml graduated cylinder. The volume occupied by the samples was recorded. Bulk density was calculated as:

Bulk density :Weight sample in grams / volume occupied by the sample

Tapped Density

Tapped density is an increased bulk density attained after mechanically a container containing the powder sample.

Tapped density : Weight of sample in grams / Tapped volume

Compressibility Index and Hausners Ratio

In recent years the compresability index and the closely related hausners ratio have become the simple, fast, and popular methods of predicting powder flow characterstics . Both the compresability hausners Ration. were determined by using bulk density and tapped density of powder .

Table no 1.4 : compresability and hausner ratio

Compresability index %	Flow character	Hausners ration
≤10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19 -1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59
≥38	Very very poor	≥1.60

Relation of flow property with HR & CI

C.I : Tapped – untapped 100 / tapped

Carrs index: Tapped density –bulk density / tapped density × 100

Angle of repose

Angle of repose has been used to characterize the flow properties of the solids. Angle of repose is characterstics related to inter particulate friction are resistance to movement between the particles. This is the maximum angle possible between surface of pile of powder or granules the horizontal plane:

Tan $^{\theta}$ = h/r

$^{\theta}$ = Tan $^{-}$h/r

Where

$^{\theta}$ = Angle of repose

h = height

r = radius

Table no 1.5 : Flow properties and corresponding angle of repose

Flow property	Angle of repose
Excellent	25-30
Good	31-35
Fair – aid not needed	36-40
Passable- may hang up	41-45
Poor – must agitate ,vibrate	46-55
Very poor	56-65

Solubility Studies

Diclofenac sodium is classified under class-2 according BCS i.e : Low solubility but high permeability. Solubility studies of diclofenac sodium were conducted at all PH ranges from 1-6.8. For this purpose of 0.1N HCL PH-4.6 Buffer, PH 6.8 buffer and 0.1%, 0.2% LDAO, Purified water was used. Highest dose of the drug i.e, 10mg was dissolved in 250ml of medium and was kept untouched for 12hrs.

Drug Excipient Compatibility Studies

The compatibility of drug and formulation components is important prerequisite before formulation. It is therefore necessary to confirm that the drug does not react with the polymer and excipients under experimental condition and affect the shelf-life of product or any other unwanted effect on the formulation.

Procedure

Drug is mixed with excipients in different ratios. These mixtures were kept in a 5ml glass white coloured vials and packed properly. These vials are exposed to:

1. Room temperature
2. 40^{0}c /75% RH.15grms of blend is prepared, which is filled in
3. vials .Observation for physical appearance are made at initial 2 weeks, 4 weeks ,the samples were determined.

Results and Discussion

FTIR Spectroscopy

The FTIR Spectrum for is shown in figure1 and in diclofenac sodium interpretation of FTIR is given in table 4. FTIR Spectrum of drug sample showed all the peaks corresponding to the functional groups present in the structure of diclofenac

sodium. From FTIR Spectrum it was concluded that the drug sample was in pure form.

Differential scanning calorimetry studies

Pure drug-diclofenac sodium polymer-eudragit s-100 binary mixture drug +polymer DSC Thermogram of diclofenac sodium is shown in the figure to .DSC Studies indicate tea sharp endothermic peak at 282^{0}C Corresponding to the melting point of the sample which matchs with the melting point of diclofenac sodium indicating the purity of drug .

UV Spectroscopy

After studing the UV spectre of diclofenac sodium it was found that drug absorbance at 226 and 276nm but maximum absorbance was at 276nm when solution is prepared in distilled water. So 276nm was considered as λmax of maximum UV Spctra of diclofenac sodium shown in figure 3.

Effect of change in PH on λmax

Λmax of drug was observed by making its solution in different PH to check the effect of PH on λmax. Result of the same is given in table 5, There was no significant change in λmax of diclofenac sodium in different PH .So calibration plot can be constructed by using distilled water and can be used for quantitative evaluation pupose through the medium of evaluation of release is phosphate buffer PH 6.8 calibration cure of diclofenac sodium.

Table-1.6 Diclofenac Sodium Nanogel (Composition of Batch A)

Composition	A-1	A-2	A-3
Diclofenac sodium(g)	100	100	100
EudragitS-100(g)	0.15	0.2	0.25
Tween-80(ml)	0.1	0.3	0.5
Glycerol(ml)	5	10	15
Carbopol(g)	0.5	0.1	0.3
Water(ml)	70	30	50
Triethanolamine (ml)	2	3	4

Table.1.7:Diclofenac Sodium Nanogel (Composition of Batch B)

Composition	B-1	B-2	B-3
Diclofenacsodium (g)	100	100	100
EudragitS-100(g)	0.15	0.15	0.15
Tween-80(ml)	0.1	0.1	0.1
Glycerol(ml)	5	5	5
Carbopol(g)	0.1	0.1	0.1
Water(ml)	30	30	30
Triethanolamine(ml)	2	2	2

Table1.8:DiclofenacSodiumNanogel (Composition of Batch C)

Composition	C-1	C-2	C-3
Diclofenacsodium(g)	100	100	100
EudragitS-100(g)	0.15	0.15	0.15
Tween-80(ml)	0.1	0.1	0.1
Glycerol(ml)	5	5	5
Carbopol(g)	0.1	0.1	0.1
Water(ml)	30	30	30
	2	2	2

Table 1.9:Interpretation of FTIR Spectrum of pure diclofenac sodium

Peakscm^{-1}	Groups
3351	O-H
1208	C-O
2936	AliphaticC-H
1179	AsymmetricC-O-C
1042	SymmetricC-O-C

Table1.10:Calibration curve values of Diclofenac sodium.

Sl.No.	Concentration (μg/ml)	Absorbance
1	0	0
2	4	0.1548
3	8	0.3173
4	12	0.4842
5	16	0.6303
6	20	0.7963
7	24	0.9237
R^2	1	
Slope	25.61	

Table1.11:Evaluation Parameters for Batch A

Evaluation parameters	A-1	A-2	A-3
Appearance	Clear	Clear	Clear
Homogeneity	Homogeneous	Homogenous	Homogenous
Particle size (nm)	165	189	213
pH	6.9±0.00	6.5±0.02	6.2±0.20
Drug content ± SD	98.8±0.02	96.5±0.02	97.8±0.04
Invitro drug release (%)	96.72±0.0784	94.75±0.963	92.78±0.77
Skinirritation test	Noirritation	Noirritation	Noirritation
Spreadability (g.cm/s)	6.3±0.5	6.7±0.6	6.0±0.6
Extrudability (g)	279±0.7	268±0.5	254±0.7
Viscosityincp at 50(rpm)	9563	8562	8000

Table1.12:Evaluation Parameters for Batch B			
Evaluation parameters	**B-1**	**B-2**	**B-3**
Appearance	Clear	Clear	Clear
Homogenicity	Homogenous	Homogenous	Homogenous
Particlesize(nm)	165	175	220
pH	6.8±0.00	6.7±0.02	6.5±0.20
Drugcontent±SD	98.8±0.02	98.5±0.02	98.8±0.04
Invitro drug release (%)	96.72± 0.0784	95.75±0.963	95.78±0.77
Skin irritation test	Noirritation	Noirritation	Noirritation
Spreadability(g.cm/s)	6.6±0.5	6.5±0.6	6.7±0.6
Extrudability(g)	279±0.7	270±0.5	260±0.7
Viscosity in cpat50 (rpm)	9863	9582	9888

Table1.13:Evaluation Parameters for Batch C			
Evaluation parameters	**C-1**	**C-2**	**C-3**
Appearance	Clear	Less clear	Clear
Homogenicity	Homogeneous	Homogeneous	Homogeneous
Particlesize (nm)	165	160	160
pH	6.5±2	6.7±1	6.2±2
Drugcontent±SD	98.2±0.029	98.6±0.04	98.5±0.072
Invitro drug release (%)	93.25± 0.903	95.72± 0.861	94.3±0.85
Spreadability (g.cm/s)	6.3	6.4	6.3
Extrudability (g)	254	243	254
Viscosity in cpat50 (rpm)	9585	9588	8500

Table1.14:Stability data of Optimized Formulation		
Time period	**Particle Size (nm)**	**Total drug content (%)**
Initial	165	98.2±0.029
After storage **(**40°C±2°Cand75%±5%RH)		
1 Month	162	95.72± 0.861
2 Month	160	94.3±0.85
3Month	164	93.25± 0.903

Table1.15:Evaluation Parameter of marketed product	
Evaluation Parameters	**Market product (Serrini)**
Appearance	Clear
Homogenicity	Homogenous
Particlesize(nm)	168
pH	6.5±0.2
Drugcontent±SD	96.8±0.02
Invitro drug release (%)	95.72±0.0784
Skin irritation test	Noirritation
Spreadability (g.cm/s)	6.6±0.5
Extrudability (g)	275±0.7
Viscosityincpat50(rpm)	9400

Stability of batches evaluation

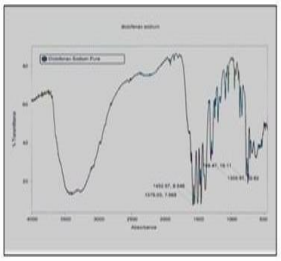

Figure 1: FTIR spectrum of pure Diclofenac sodium

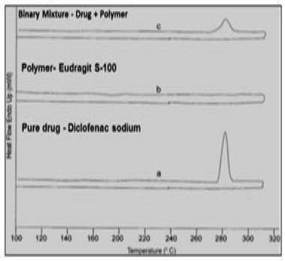

Figure 2: DSC thermogram of diclofenac sodium+polymer+binary mixture

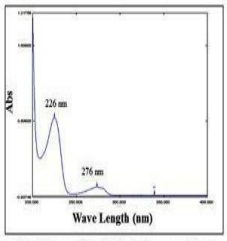

Figure 3 : UV spectra of Diclofenac sodium

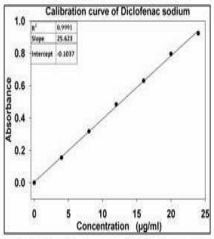

Figure 4: Calibration curve of Diclofenac sodium

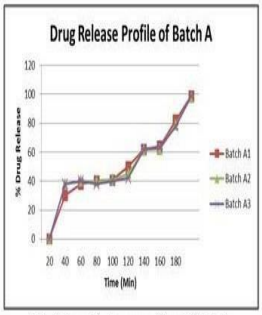

Fig.5 Drug Release profile of Batch A

The stability studies were carried out on optimized formulation. The sample were stored at 40^{0}C ±2^{0}C and 75%±5% relative humidity for 3 months as per ICH guidelines .After 1,2 and 3 months samples were withdrawn and tested for appearance, PH, particle size, drug content, spreadibility ,extrude ability, viscosity.

Stability Data of Optimized Formulation

The evaluation parameter performed for the trial batches (B and C) are the same as done for the above prototype batch (A) and they are appearance, homogeneity, particle size measurement, PH measurement, drug entrapment efficiency, drug content, invitro drug release, skin irritation study,

spreadibility, extrude ability, rheological study, stability batches form the evaluation parameters results of trial batches the found batch A1 as the optimized batch and further experimental designs formulated figure 5. And shown in table 10. Gel formation, formulation got converted into the gel phase and thus drug release became slow. The results showed that the formed gel shad the ability to retain diclofenac sodium for the duration. The production of the formulation is also proved to be better and cost effective in comparison with oral dosage forms.

Conclusion

Nanogel formulation containing Diclofenac sodium was successfully prepared and Shows effective as well as better carrier for the transdermal/topical preparations the Formulate dnanogel was optimised for homogenicity, particle size, Ph, drug content, In vitro drug release ,skin irritation test, spreadability, extrudability, and viscosity. Administration of this through dermal route bypass the disadvantages of oral route And maintain the consistently plasma for the therapy for single dose. The initial release Rate from each formulation was very rapid, this may be due to incomplete gel formation in the earlier time period, but there release becomes low in latter period after complete Gel formation. The release profile sex habited an inflection point, which indicated gel formation on the diffusion membrane in donor compartment of diffusion cell. During gel formation, formulation got converted into the gel phase and thus drug release became slow. The results showed that the formed gel shad the ability to retain diclofenac sodium for the duration. The production of the formulation is also proved to be better and cost effective in comparison with oral dosage forms.

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Conflict of Interest

Authors are declared that no conflict of interest.

Ethical Statement

Not required

Author Contribution

All authors are contributed equally.

Informed Consent

Not required

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