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Development, optimization of microemulsion based Transdermal gel for NSAIDs Drug

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A B S T R A C T

The present research work is based on the formulation and evaluation of topical gel of etoricoxib where Carbopol 940, tween20, span20 is used as the polymer. Gels were prepared by dispersing the polymers in a mixture of water and glycerine with propyl paraben as the preservative and the varying amount of etoricoxib, being kept under magnetic stirring until the homogeneous dispersion was formed. The dispersion was then neutralized and made viscous by the addition of triethanolamine. The tween20, span20 gels of etoricoxib were found to be homogenous with good drug loading. The pH of all the gel formulations was found within the neutral pH range which is compatible with skin. And the viscosity of the formulations was found to be feasible for topical drug delivery. The drug content of the three formulations was found in the range of 88.3% to 98% which shows efficient drug loading. Results of In vitro drug release study showed that F3 formulation has better diffusion of drug through membrane The compatibility study showed that the major peaks in FT-IR spectra of the pure drug were found to be intact in their physical mixture. Hence there is no interaction between drug and tween20, span20 in their physical mixture. Tween20, span20 can be effectively used as the polymer for topical gel preparation. And F3 formulation containing 1.2 % w/w Tween 20 and 1.8% span 20 may be effectively used as topical transdermal delivery for etoricoxib.

Keywords: Etoricoxib, Transdermal Gel, Drug release, Compatibility study HCl, microemulsion, HPMC, Carbopol940.

A R T I C L E I N F O

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C O N T E N T S

1. Introduction

Recent technological advancements have rendered transdermal medicine delivery systems a viable option for patient dosing. Among the numerous benefits of transdermal medication delivery are the avoidance of digestive system clearance and the initial pass-through hepatic metabolism. A significant portion of failed attempts at oral medication delivery (74%) can be attributed to various factors. The skin, acting as a protective barrier, possesses self-healing capabilities in case of compromise [1].The utilization of transdermal medication administration has witnessed a surge in popularity in recent years. This method has gained favor due to its ease of use and the generally positive safety reputation of the drugs involved. Transdermal drug delivery stands out as a practical choice, characterized by its reliability, simplicity, security, and cost-effectiveness. For oral intake, a higher drug content in the dose form may be necessary due to potential loss mechanisms. Incorrect administration of medication has the potential to cause harm, making it crucial to consider alternative delivery methods. Conventional drug delivery techniques may result in concentrations lower than the minimum effective concentration (MEC). In any health situation, maintaining an adequate supply of MECs is vital. Conventional technologies may fall short in achieving the

required low concentration, but novel medication delivery strategies (such as transdermal and regulated methods) offer promise. Transdermal drug delivery systems aim to localize pharmaceutical administration and regulate the distribution rate, providing advantages like controlled absorption into the circulation when medications are applied to healthy skin [2].

Nanoemulsions represent colloidal dispersions consisting of an oil phase, aqueous phase, surfactant, and co-surfactant in precise proportions. In contrast to coarse emulsions requiring external energy for micronization, nanoemulsions rely on low interfacial tension. The addition of a co-surfactant facilitates the spontaneous formation of a thermodynamically stable nanoemulsion. The droplet size in the dispersed phase is notably small, typically below 10-200 nm in diameter, resulting in transparent liquids. While nanoemulsions theoretically offer diverse drug delivery routes, the topical application of nanoemulsions has garnered increasing attention [3]. The transdermal permeation of drugs is influenced by three primary factors: drug mobility in the vehicle, drug release from the vehicle, and drug permeation into the skin. Nanoemulsions enhance the transdermal delivery of various drugs compared to conventional topical preparations such as emulsions and gels. The mobility of drugs in nanoemulsions is more efficient compared to nanoemulsions with gel formers, which increase viscosity and hinder skin permeation [4-6]. The superior transdermal flux achieved with nanoemulsions is primarily attributed to their high solubilization potential for both lipophilic and hydrophilic drugs. This heightened thermodynamic activity towards the skin has been demonstrated to enhance transdermal drug delivery. Nanoemulsions emerge as excellent carriers for the topical delivery of highly lipophilic drugs, as evidenced by the application of ketoprofen, a widely used non-steroidal anti-inflammatory drug (NSAID) in rheumatism treatment [7-11].

2. Materials and methods

Materials: Etoricoxib was obtained as a gift sample from Biomedica Remidies, Ludhiana. Carbopol 940, HPMC, Liquid paraffin, Tween 20, Span20, Glycerin, Propylparaben were taken from Lobachemie Pvt.Ltd. Mumbai.

Methods:

Determination of λmax

A solution of Etoricoxib containing conc. 10µg/ml was prepared and UV- Spectrum was taken using Shimadzu (UV- 1900i) spectrophotometer. The solution was scanned in the range of200-400nm[12-14].

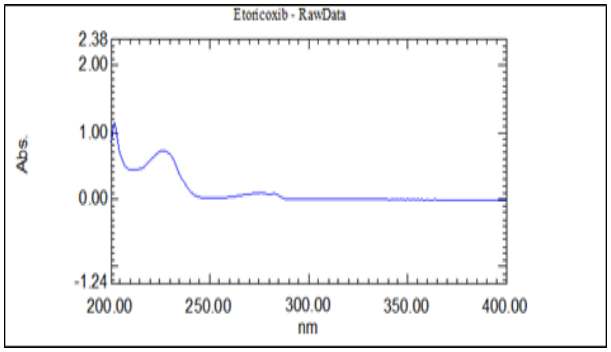

Fig.1 standard calibration curve standard calibration of Etoricoxib

Accurately weighed 100 mg of Etoricoxib was dissolved in 100 ml of 7.4 Phosphate buffer(Standard Stock solution). From the above solution 10 ml was pipetted and diluted to 100ml with & 7.4 buffer (Stock I)[15-18]. From this solution aliquots were prepared of 1.0, 2.0, 3.0, 4.0, 5.0ml into 10 ml volumetric flask with phosphate buffer 7.4 to satisfy the Beer's range of 2-100µg/ml. Absorbance read at UV-VIS Spectrophotometer at 233 nm against blank (phosphate buffer 7.4). The calibration curves of Etoricoxibare shown in Figure 1.

Method

Etoricoxib microemulsion based gel was prepared by using the above formula with different concentrations. The formulation that contains carbopol involves the soaking of carbopol to swell up in the calculated amount of deionized water. And HPMC was dispersed in the purified water. Gel was shaken well with help of a stirrer pH was adjusted to 6 – 6.5 using Triethanolamine [19-21]. The oil phase of the emulsion was set up by dissolving light fluid paraffin while the watery phase was set up by dissolving tween 20 in refined water. Propyl paraben is dispersed in propylene glycol and mixed with the oil phase. And then the drug was dissolved in the above solution. Then warmed at 70–80ºC, at that point the sleek stage was added to the way stage [22-26].The current study will be carried out for its physicochemical properties of appearance, dropletsize and size distribution, morphology, pH value, and rheology were characterized. In vitro permeation was carried out to assess the enhance menta cross and into the skin. Evaluation of physicochemical properties of formulated transdermal gel such as, Determination of λmax, Physical appearance, Determination of pH, Homogeneity, Viscosity, Spreadability, Extrudability, In-vitro diffusion study, FTIR study, Stability studies [27-30].

Table 1: Formula to prepareemul gel of Etoricoxib

Ingredients % w/w	F1	F2	F3	F4	F5	F6	F7	F8	F9
Etoricoxib	100	100	100	100	100	100	100	100	100
Carbopol 940	0.5	0.5	0.5	0.5	-	-			0.25
HPMC	-	-	-		0.5	0.5	0.5	0.5	0.25
Liquid paraffin	5	5	5	5	5	5	5	5	5
Tween20	2	1.6	1.2	2	1.6	1.2	1.5	2	1.8
Span20	3.6	2.4	1.8	3.6	2.4	1.8	2.5	3.6	3.5

Glycerin	8	8	8	8	8	8	8	8	8
Propylparaben	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
Water QS	100	100	100	100	100	100	100	100	100

3. Results and Discussion

Table 2: Evaluation Solubility studies

Trial	Solubility(µg/ml)
Trial1	76.58
Trial2	77.99
Trial3	78.00
Average+Stdev	77.52±0.816

Determination of lipophilicity, hydrophilicity and partitionco efficient of ETC:

Physicochemical studies of Etoricoxib were conducted to evaluate the physicochemical properties of drug. Studies were conducted to evaluate ETC hydrophilic and lipophilic compatibility. Result shows that ETC having solubility potential of nearly 3.881±0.374 that can be closely correlated to the reports recorded in the research literatures.

Table 3: Lipophilicity, hydrophilicity

S.no	**Trials**	**Log p**
01	Trial1	3.8440
02	Trial2	3.9188
03	Trial3	3.8786
Average of triplicate trials (n=3)		3.881±0.374

Table 4: WavelengthofmaximumabsorptionofETCin7.4 pH buffer

SI. No	**Solvent.**	**λmax**
1.	7.4pH buffer	233nm

Table No.5: Absorbance data for the standard calibration curve of ETC in 7.4 pH buffers at 233 nm

Conc. inµg/ml	**Abs**
0	0.000
2	0.113±0.013
4	0.201±0.008
6	0.307±0.017
8	0.412±0.022
10	0.514±0.006

Table 6: Determination of pH, Spreadability, Extrudability and Drug content

Formulations	**pH**	**Spreadability (g.cm/sec)**	**Extrudability (g.cm/sec)**	**Drug content (%)**
F1	6.54±0.058	32±0.255	29±0.095	96.18±0.065
F2	6.38±0.087	29±0.189	35±0.112	96.66±0.122
F3	6.87±0.155	21±0.345	44±0.256	98.14±0.073
F4	6.86±0.138	36±0.382	46±0.202	94.53±0.104
F5	7.05±0.104	46±0.333	48±0.178	95.22±0.042
F6	6.36±0.143	53±0.564	50±0.188	96.69±0.125
F7	6.33±0.164	52±0.128	50±0.294	88.35±0.087
F8	6.87±0.106	60±0.127	78±0.065	92.37±0.066
F9	7.04±0.094	32±0.260	76±0.163	93.77±0.115

TheformulatedformulationsofemulgelsweresubjectedtothepH,Visocsity,andSpreadability, Extrudabilty and drug content determination as per the methodology describe in the section 5.3.4, 5.3.6, 5.3.7, 5.3.8., 5.3.9, respectively. The pH of the formulations found to be in the range of 6.3–7. The Spredability of F1 – F8 formulations found to be in the range of 21–60 g. cm/sec. The extrudability found to be in the range of 29–78. Drug content of the formulations is found to be in the range of 88.3-98.

Table no7: In-vitro drug release of ETC micro emulsion based gel

Time in min	% Cumulative drug release								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
15	9.63±0.090	12.66±0.039	18.25±0.069	21.66±0.054	6.32±0.072	11.36±0.075	12.30±0.084	25.62±0.077	32.64±0.060
30	18.83±0.085	25.61±0.082	29.59±0.114	33.83±0.101	12.34±0.109	35.98±0.112	24.66±0.106	38.54±0.099	44.23±0.088
60	21.62±0.146	42.13±0.144	45.66±0.160	42.62±0.131	21.03±0.145	56.23±0.115	32.58±0.128	46.32±0.119	56.27±0.140
90	32.66±0.114	51.29±0.066	59.22±0.162	56.37±0.098	33.16±0.071	68.90±0.083	43.26±0.122	58.36±0.090	68.32±0.083
120	58.83±0.083	52.37±0.053	68.73±0.095	61.29±0.068	41.24±0.082	78.81±0.161	56.39±0.085	72.53±0.108	75.17±0.062
150	72.41±0.065	72.88±0.114	89.52±0.073	71.73±0.085	56.23±0.073	83.68±0.107	62.61±0.059	81.23±0.132	86.82±0.083
180	88.23±0.102	81.11±0.081	99.49±0.117	82.63±0.108	63.02±0.110	92.17±0.101	86.88±0.098	89.56±0.103	90.15±0.118

Table no: 8 optimization central composite design formula

		Factor 1	Factor 2	Response1
Std	Run	A: Tween	B: Span	DrugRelease
		%	%	%
6	1	2	3.6	88.23
3	2	1.6	2.4	81
9	3	1.2	1.8	99
2	4	2	3.6	82
7	5	1.6	2.4	63
1	6	1.2	1.8	115
5	7	1.5	2.5	86
4	8	2	3.6	89
8	9	1.8	3.5	90

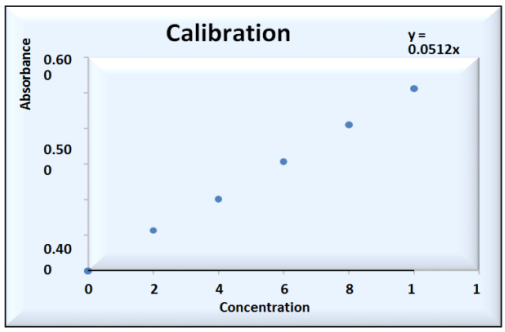

Fig.2: Standard plot for Etoricoxib in 7.4 pH buffer

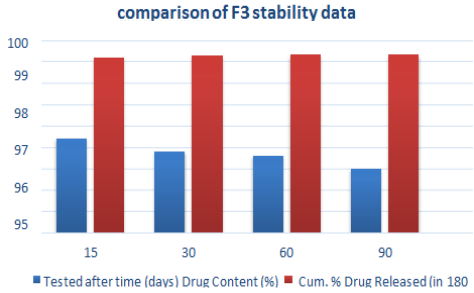

Fig.3 Comparison of Drug content and % CDR in stability studies of micro emulsion based gel from F3 on fifteen-day, one month, two month, and three month of accelerated stability studies.

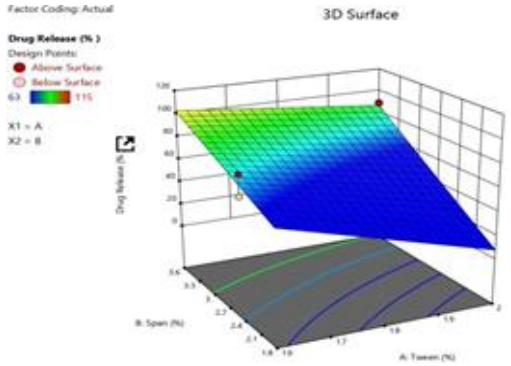

Fig.4. Post analysis

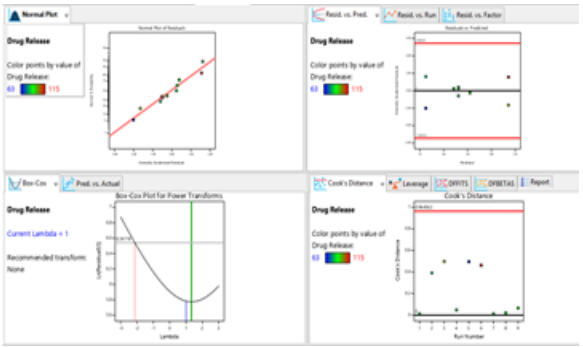

Fig. 5. Post analysis

4. Conclusion

Etoricoxib is a COX-2 inhibitor with a high degree of selectivity for its target. It provides an alternative to other selective and traditional NSAIDs in treating patients with arthritis and other painful conditions. Etoricoxib may be given to a broad range of patients without need for dosage adjustment, except in cases of hepatic insufficiency. It is suitable for once-daily administration, which may facilitate patient compliance with treatment. Clinical trials have shown that etoricoxib has at least comparable efficacy and greater gastrointestinal to lerability compared with nonselective NSAIDs, and may therefore be particularly suitable for patients with gastrointestinal risk factors. In summary, etoricoxib provides an effective therapeutic alternative in the management of arthritic and painful conditions. As for all drugs, the benefits and risks of treatment should be evaluated carefully for each patient. Microemulsiongelofetoricoxibwerepreparedbysimplemetho d.Variousevaluationparameterwasperformed.Inpreviouscha pterevaluationandpreparationofformulationshavebeendiscus sedindetail.Fromthe study it can be concluded that, Tween20andspan20canbeusedfortheformulationofmicroem ulsionbasedgel. FTIR study indicates that there is no interaction between etoricoxib and polymers and the drug was compatible with the formulation components. The physical appearance of F1 - F9 was found to be creamy white with no grittiness in it. The in-vitro drug release study of the formulations from F1 – F9 is found to be in the range of 81–115.02%. The F3showed best % CDRupto99.22%. Thesimilarityfactoranddissimilarityfactorweredeterminedby consideringtheoptimized batch as reference standard and reproducibility batch is considered as trials. The results found that the batches have shown more similarity and less dissimilarity. From stability studies, it was noted that surface was free of any kind of microbial or fungal growth or bad odor. No changes in the physical parameters of microemulsion based gel were noted. The drug content of the formulations was found 98.50% for batches of F3, which shows that, there is no decrease in drug content and difference is insignificant. The overall fit of the curve into various mathematical models was discovered to be on average. By comparison, of drug content and % CDR in stability studies of microemulsion gel from F3 on fifteen-day, one month, two month, and three month of accelerated stability studies was found that after a period of three month of storage there were no changes in the physical, as well as drug release profiles of the emulgel of both the batches and both, were imitating the same drug release pattern.

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