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INVESTIGATING THE ANTI INFLAMMATORY ACTIVITY OF ETODOLAC LOADED EMULGEL : FORMULATION , DEVELOPMENT AND IN- VITRO / IN-VIVO EVALUATION

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ABSTRACT

The goal of this research was to develop etodolac loaded emulsion for prolonged release of medicine and incorporate it in to topical gel delivery system to lessen the adverse effects by site specific targeting. The present investigation focused on the formulation of etodolac emulgel and the influence of permeation enhancers such as Piperine,Peppermint Oil and Clove Oil. Etodolac emulgel was created by emulgel method by employing various excipients such as polymers as carbopol-940,Carbopol-934, Carbopol-974P, propylene glycol, tween20, and span20 and with penetration enhancers such as piperine , peppermint oil and clove oil. The prepared emulgel was assessed for its qualities Further the investigation of release mechanism was carried out by fitting the drug release data to various kinetic equations like zero order, first order, higuchi's and korssmeyerpeppas equations and from the values so obtained, the best fit model were arrived at. From the a forementioned results formulation F2 and F4 was found to be optimum formulation for the topical release of etodolac that conformed with all the parameters. It releases 72.26±0.98 % of medication in 8 h time. It follows the higuchi's of drug release kinetics. Also, stability upon storage for 3 month at room temperature, where no significant change was detected in the parameters examined including color, consistency, pH, rheological characteristics, skin permeability and drug release pattern. Therefore, it was determined that etodolac emulgel formula could be extremely promising topical replacement for the standard dose form give sustained and prolonged distribution of medicine.

Keywords- *anti inflammatory, activity, etodolac, emulgel,*

INTRODUCTION

An injury caused by any substance can cause inflammation, which is defined as the local reaction of living mammalian tissues to the injury. It is a defense mechanism that the body employs in order to eradicate or restrict the spread of the harmful agent, which is then followed by the removal of both the necrotic cells and tissues. "Immunity" or "Immune reaction" and the inflammatory response by the host are both considered to be protective mechanisms in the body. Inflammation is the apparent response to an immune reaction, and the activation of the immune response is almost needed before the inflammatory response emerges. Multipherubtorces are released by injured tissues which are induced by severe secondary changes in surrounding uninjured tissue. These changes are referred to as inflammation. When tissue injury occurs, whether it is caused by bacteria, trauma chemicals, heat, or any other phenomena, multipheluborces are released. It is possible to describe a gel as a semi-solid formulation that possesses an exterior solvent phase, a polar (organogel) or polar (hydrogel) immobilized within the gaps that are available in a three-dimensional networked structure. Organogels are different types of gels that are derived from non-aqueous liquids. These gels have been recognized in a number of Pharmacopoeias as potential topical delivery systems for lipophilic pharmaceuticals. As a result of their lipophilic nature and occlusive action being amplified by the presence of a penetration enhancer, organogels are not only capable of exerting a local effect, but they are also capable of achieving a systemic effect by percutaneous absorption.

Etodolac is classified as a BCS Class II medication. Due to the fact that it is a selective COX-2 inhibitor with a selectivity that is ten times greater for COX-2 than it is for COX-1, it is safe to prescribe for the treatment of acute pain and inflammation. Etodolac has a negative water solubility and a high hydrophobicity, both of which contribute to its low permeability. Etodolac is known to irritate the stomach and produce a variety of unpleasant side effects when taken orally, including constipation, diarrhea, vomiting, headache, dizziness, sore throat, and blurred vision. As a result, there are bounds to the formulation of oral dosage forms. The creation of a topical drug delivery system is made more difficult by the presence of such substances. This research was conducted with the purpose of developing and analyzing stable organogel formulations that contained etodolac. Organogels are made out of a mixture of sesame oil as the oil phase, span 80 and tween 80 as the organogelator, and an aqueous phase in the necessary proportions. Carbopol is used as a consistency modifier, and methyl and propyl paraben are used as preservatives. The distribution of medications through the skin utilizing these organogels boosts the local and systemic delivery through a variety of methods, which makes them appropriate vehicles for the delivery of anti-inflammatory compounds. In order to accomplish these goals, the organogel was examined for its behavior in terms of the influence of pH, rheological properties, gel so transition research, spreadability, in-vitro drug release, globule size, extrudability, drug content, ex-vivo release, and skin irritation study. Using carrageenan-induced paw edema, the anti-inflammatory effect of a selected formulation including etodolac was assessed and compared with the gel formulation that is currently on the market (Proxym gel).

OBJECTIVES

- Formulate Etodolac- Loaded Emulgel With Optimized Characteristics. Evaluate The In-Vitro Release Profile For Sustained Drug Delivery.

- Access The In-Vivo Anti-Inflammatory Activity Of The Emulgel Using Suitable Animal Model.

Emulgels

Emulgel is the name given to the type of medicine that is administered when a combination of gel and emulsion is utilized. Gels, particularly hydrogel formulations, are increasingly receiving consideration for the topical application of medications. This is due to the fact that gels have a captivating appearance and expand to provide a pleasant and refreshing sensation. Emulgels are produced and used to overcome this constraint, so that even a hydrophobic medicinal moiety can have the particular features of gels. Gel formulations' pharmacological activity cannot alter as easily as the solution process does. Emulgels are used to overcome this constraint. The mixture of emulsion and gel that is known as eumlgels is a type of hydrogel that contains microdroplets of oil that are dispersed in a random assortment. In addition, they are emulsions. They can be of the o/w or w/o form, and they are gelled by combining with a gelling agent. In recent times, they have been utilized as carriers for the transportation of a variety of medications and substances into the vagina and the skin.

METHODOLOGY

Preformulation studies

There are exploratory practices that begin in the beginning phases of the formulation production process, and studies of preformulation pertain to those practices. Studies on preformulation are conducted with the purpose of classifying the bulk material, determining whether or not the initial excipients are compatible with the active ingredient, and enhancing analytical procedures that will be utilized throughout the creation of formulations. The following are the objectives of the program:

The mixture of emulsion and gel that is known as eumlgels is a type of hydrogel that contains microdroplets of oil that are dispersed in a random assortment. In addition, they are emulsions. They can be of the o/w or w/o form, and they are gelled by combining with a gelling agent. In recent times, they have been utilized as carriers for the transportation of a variety of medications and substances into the vagina and the skin.

- It is necessary to ascertain the physicochemical properties that are necessary for a novel medicinal compound.
- Locating the profile of its kinetic volume is the goal here.
- Finding out what its physical characteristics are.
- to determine whether or not it is compatible with the excipients.

The preformulation studies that are performed on the drug sample that has been gathered consist of color, measurements, analyses of the solubility, evaluations of the melting point, and compatibility tests.

Solubility

A little amount of the medication, approximately one to two milligrams, was placed in a separate test tube. Then, five milliliters of a solvent consisting of water, ethanol, methanol, 0.1N hydrochloric acid, 0.1N sodium hydroxide, chloroform, and a 7.4 pH buffer was added to the mixture. The mixture was shaken violently and allowed to sit for a period of time. Pay attention to the degree to which the product is soluble in a variety of solvents when it is at room temperature.

Melting point determination

In order to determine the melting point, a digital capillary melting point device was utilized.

Partition coefficient

One example of a product's ability to move cell membranes, along with octanol/water and chloroform/water, is the oil/water partition coefficient in technique. This is a computation of the lipophilicity of the product, and it is also an example of its capacity to move cell membranes. The ratio of unionized medicine that is distributed in equilibrium between the organic and aqueous phases is what is meant to be understood by the terminology of the partition coefficient. Furthermore, it offers a method for describing the lipophilic and hydrophilic properties of the medication.

Procedure

After ensuring that the separating funnel was thoroughly cleaned and dried, the octanol/water method (50:50 20ml) was poured into the separating funnel in an adequate quantity, and then the 10mg of medication was added to it. A continual shaking of the funnel was performed until the drug was distributed in an equal manner in both processes. Then, in order to allow each of the phases to be settled, it is placed on stand. Following the separation of both phases in the beaker, UV spectroscopy (IP, 2010 and SB Shirsand et al., 2012) is performed to determine the amount of medication that was present in each step.

Drug excipients compatibility studies

After combining the drug with the excipients and polymer, an application of (ETO) powder that had been mixed with potassium bromide and pressed into the shape of a disc was carried out. This was done in order to investigate whether or not there were any changes in the chemical composition of the drug after it had been

combined with the excipients and polymers. In order to evaluate the disk, Shimadzu FTIR spectroscopy (4000-400) cm-1 was utilized.

Standard calibration curve for etodolac

The whole volume of methanol was brought up to 100 milliliters, and 100 milligrams of ETO was accurately measured and dissolved in a little amount of methanol. It was pipetted out of this primary solution 10 milliliters, and then 100 milliliters of a saline solution with a pH of 7.4 that was buffered with phosphate was added. Aliquots were extracted from this secondary solution in order to acquire a concentration ranging from 2 to 10 micrograms per milliliter. At a wavelength of 279 nm, the absorbance of the solution that was produced was determined by the UV-visible Spectrophotometer (Shimadzu) by employing phosphate buffered saline with a pH of 7.4 and a little amount of methanol as the blank. The standard curve was produced by plotting the concentration along the X-axis and the absorption along the Y-axis.

Formulation

Preparation of emulsion phases

For the preparation of the oily phase of the emulsion, span-20 was dissolved in methanol in light liquid paraffin, along with the required amount of etodolac. For the purpose of increasing the rate of penetration, it was mixed with piperine , clove oil and peppermint oil. Tween-20 was dissolved in distilled water, which resulted in the preparation of an aqueous procedure. Through the use of propylene glycol, methyl paraben was dissolved after being coupled with an aqueous phase.

Preparation of gel

In a beaker that had been dried out beforehand, a quantity of carbopol-940 that had been precisely weighed was added to ten milliliters of distilled water. Regular stirring with a mechanical shaker was used to ensure that it was thoroughly mixed. More distilled water was added in order to maintain the gel's consistency. As a result of the addition of triethanolamine, the pH of the formulation was adjusted from 5.0 to 6.0.

Formulation of Emulgel

Following the heating of the oily and aqueous phases to temperatures ranging from 700 to 800 degrees Celsius in isolation, the mixture was then mixed with continuous stirring and allowed to cool to room temperature. In order to obtain the formulation of the etodolac propionate emulgel and to prepare a distinct formulation, the emulsion that was formed was mixed with the gelling agent carbopol 940 (or Carbopol 934) in a ratio of 1:1 while being gently stirred.

Evaluation of Emulgel

Physical characteristic

Visual examinations were performed on the emulgel formulations that were produced to determine their pH, color, homogeneity, purity, grittiness, stiffness, and the distinction between two phases.

Determination of pH

For the purpose of determining the pH of the emulgel formulations, electronic pH meters were utilized. The electrode was submerged in the gel formulation for a period of thirty minutes, during which time one gram of gel was dissolved in twenty-five milliliters of filtered water. This process continued until a continuous reading was achieved and a steady reading was noticed. (Jain A et al., 2010) The pH of each formulation was measured three times, and the average values were estimated after the measurements were considered.

Washability

After applying formulations to the skin, manual testing was performed to determine how easy it was to wash with water and how long it would take.

Extrudability study

It is possible to line the formulations of the emulgel with collapsible metal tubes or collapsible aluminum tubes. In order to extrude the material, the tubes were pressed, and the extrudability of the formulation was evaluated (Gupta GD et al., 1999).

RESULTS AND DISCUSSION

The current investigation aimed to create and characterize a topical medication delivery system that is capable of effectively delivering etodolac over the skin. It has a low water solubility and a poor dissolution, making it an unsuitable option for the oral route of administration. Therefore, an innovative method of synthesizing hydrophobic medicines, known as emulgel, was explored. This method involved the incorporation of emulsions into gels in a straightforward manner. By integrating hydrophobic medications into emulsion form, which further aids in boosting their skin permeability, it is possible to improve the solubility of these drugs.

In the current study, six novel emulgel formulations of etodolac were effectively constructed and assessed on a variety of criteria. These formulations were created by combining emulsifiers such as Span 20 and Tween 20 with gelling agents such as Carbopol 934 , Carbopol 940 and Carbopol 974P. All of the batches' physicochemical properties, including pH, viscosity, extrudability, and drug content, are displayed in Table 1. Other metrics include drug content. In every single one of the emulgel testing, it was discovered that the emulgel was homogeneous, and the smears were transparent, without any grittiness or particles present. The pH values

of the batches of emulgel were found to fall within the range of 6.8-7.1, which is comparable to the pH of the skin. Due to the fact that it influences both the extrudability and the release of the medication, the viscosity of the emulgels is an essential characteristic for their characterization. All of the formulations were found to have a viscosity range that was between 17000 and 55000 cps.

Table 1: Physicochemical characterization of etodolac emulgel

Formulation Code				Parameters		
	Nature	pH	Viscosity (cps)	Spread ability gm cm/sec	Drug content (%w/w)	Extrudability
EG1	White, Homogenous	5.20	43600	1.50±0.18	73.45±0.09	++
EG2	White, Homogenous	5.02	48600	1.50±0.09	88.63±0.15	+++
EG3	White, Homogenous	5.30	42700	1.65±0.44	74.12±0.22	++
EG4	White, Homogenous	5.81	43600	1.90±0.21	84.40±0.18	+++
EG5	White, Homogenous	5.59	46300	1.60±0.27	76.77±0.52	++
EG6	White, Homogenous	5.81	42200	1.35±0.15	65.13±0.08	+++
EG7	White,	5.18	44700	1.45±0.19	71.83±0.12	++

	Homogenous					

During the application process and for the patient's compliance, the extrusion of the emulgel from the tube is a vital action to complete. Emulgels that have a high consistency could not be able to be easily extruded from the tube, but emulgels with a low viscosity might be able to be extruded from the tube more quickly. Extrudability was evaluated for each and every formulation, and it was found to be satisfactory. Upon analysis, it was determined that the percentage of drug content in all formulations was satisfactory, falling within the range of 65.54±0.52 to 88.74±0.08%.

Up until twenty-four hours after the exposure, rats did not exhibit any allergy symptoms such as inflammation, redness, irritation, erythema, or edema symptoms. Figure 1 illustrates the drug release characteristics of etodolac emulgel formulations when tested in vitro. At the conclusion of 120 minutes, the emulgel formulations of batch EG2 showed the highest possible drug release of 72.26%, while batch EG1 demonstrated the lowest possible release of 45.15%. Table 2 contains information regarding the kinetics of drug release from the emulgels.

Table 2: Drug release (%) kinetic parameters for different etodolac emulgel formulations

0 min	0	0	0	0	0	0	0
15 min	6.41	15.91	8.51	7.11	16.12	7.65	18.26
30 min	13.31	23.34	20.97	25.67	23.12	18.95	36.27
45 min	16.27	33.73	30.35	35.11	28.26	23.12	45.21
60 min	28.31	55.13	45.27	50.31	45.11	34.46	52.12
90 min	30.67	65.12	50.32	61.45	47.11	45.21	60.16
120 min	45.15	72.26	62.12	66.26	56.24	58.96	63.76

Table3: Higuchi model of zero order, 1st order kinetics along with Korsmeyer-Peppas Model

Batch Code	**Zero order model**	**First order model**	**Higuchi model**	**Korsmeyer-Peppas model**

	R	K	R	K	R	K	Slope(n)	R	K
EG1	0.8976	3.6372	0.9555	-0.0549	0.9846	10.3551	0.6248	0.9981	7.8464
EG2	0.9682	2.6368	0.9562	-0.0358	0.9783	8.8968	0.7077	0.9977	4.7338
EG3	0.9657	2.0245	0.9581	-0.0252	0.9274	10.3922	0.8265	0.9946	2.8082
EG4	0.8561	4.2172	0.9345	-0.0783	0.9758	8.9453	0.5721	0.9984	11.5966
EG5	0.9345	2.6465	0.9548	-0.036	0.9368	10.4181	0.6184	0.9937	7.1578
EG6	0.9621	2.0239	0.9563	-0.0292	0.9682	8.6137	0.7018	0.9954	4.5348

The acute inflammatory reactions, such as edema, that are induced by the local injection of carrageenan into the hind paw of rats are described. It has been defined as a biphasic event22 that the development of the edema that was generated by carrageenan comes about. The concerted release of histamine, bradykinin, 5-hydroxytryptamine, or cyclooxygenase products can cause a fast early phase that can last for up to two hours. And a more prolonged late phase that lasts between two and five hours is controlled by neutrophil infiltration and the sustained generation of arachidonic metabolites (prostanoids) (mainly by cyclooxygenase) or nitric oxide from inducible nitric oxide synthase23. According to Table 3, the emulgel formulation of batch EG2 demonstrates a mean paw volume percentage inhibition of 18.59%, while the standard indomethacin demonstrates a mean inhibition of 54.861%.

Table 3: % Inhibition on carrageenan induced paw volume by different treatment

Treatment	Percent inhibition of paw oedema					Mean of % Inhibition
	1 hr	2hr	4hr	6hr	8hr	
Standard (10mg/kg, I.P. Indomethacin)	12.87	21.39	31.79	39.41	47.83	54.86
Etoricoxib emulgel, EG1, 2 gm	4.20	5.12	6.06	11.07	13.51	18.597

N = 6, $p < 0.05$

Prakash et al. conducted a study in which they investigated the effectiveness of topical etodolac emulgel as an anti-inflammatory agent for a period of six hours. This study was checked over a period of eight hours in order to observe the changes for a longer period of time, twenty-four hours. EG2 demonstrates a mean percentage inhibition of paw thickness of 18.986%, whereas indomethacin was found to have a mean percentage inhibition of 29.91% (Table 4).

Table 4: % Inhibition on carrageenan induced paw thickness by different treatment

Treatment	Percent inhibition of paw thickness					Mean of % Inhibition
	1 hr	2hr	4hr	6hr	8hr	
Standard (10mg/kg, I.P. Indomethacin)	15.08	18.89	22.61	25.23	27.74	29.91
Etoricoxib emulgel, EG1, 2 gm	3.19	5.42	11.37	14.13	16.81	18.98

N = 6, p< 0.05

CONCLUSION

The formulation of etodolac emulgel and the influence of natural permeation enhancers like piperine , peppermint oil and clove oil were the primary focuses of the current research. A variety of excipients, including polymers like carbopol-940, propylene glycol, tween20, and span20, as well as penetration enhancers like piperine,peppermint oil and clove oil were utilized in the preparation of etodolac emulgel through the use of the emulgel method. A thorough examination of the emulgel'scharacteristics was carried out. In addition, the investigation of the release mechanism was carried out by fitting the data on drug release to a number of different kinetic equations, such as zero order, first order, higuchi's, and korssmeyerpeppa's equations. Based on the values that were obtained, the model that provided the best match was determined. As a result of the findings shown above, formulation F4 was determined to be the most effective formulation for the topical release of etodolac, conforming to all of the applicable parameters. After eight hours, it releases 72.26±0.98 percent of the medication. In terms of drug release kinetics, it adheres to the Higuchi's model. Additionally, stability was observed when the product was stored at room temperature for a period of three months, during which time

there was no discernible change in the parameters that were tested, including color, consistency, pH, rheological properties, skin permeability, and drug release characteristics. As a result, the conclusion that was reached was that the etodolac emulgel formulation has the potential to be a very promising topical alternative to the conventional dosage form that promises to provide sustained and prolonged drug administration.

REFERENCES

- Kumar P. Etoricoxib-induced pretibial erythema and edema. Indian Dermatol Online J 2015; 6 (Suppl 1): S47–9.
- Yadav S, Wairkar S, Invally M, Ranade S. Topical emulgel of tolnaftate with penetration enhancer: development, characterisation and antifungal activity. Indian J Med Res Pharm Sci 2017; 4(10): 28-35.
- Parmpreet S, Sunny K, Rajni B and Naresh S. Development and characterization of clindamycin phosphate emulgel for topical delivery. Int J Recent Adv Pharm Res 2014; 4(3): 47- 62.
- Parmpreet S, Sunny K, Rajni B and Naresh S. Development and characterization of clindamycin phosphate emulgel for topical delivery. Int J Recent Adv Pharm Res 2014; 4(3): 47- 62.
- Bacchi, S., et al., Clinical Pharmacology of Non-Steroidal Anti-Inflammatory Drugs: A Review. Vol. 11. 2012. 52-64.
- Davis, J.S., et al., Use of non-steroidal anti-inflammatory drugs in US adults: changes over time and by demographic. Open heart, 2017. 4(1): p. e000550.
- Gopinath R., Naidu R.A.S., 2011. Pharmaceutical Preformulation studies – current review. Int J Pharm Biological Arc, Vol. 2, Issue 5, pp. 1391-1400
- Gupta GD, Gaud RS. Release rate of Tenoxicam from Acrypol gel. The Indian Pharmacist 2005; 69-76.
- Nair R, Sevukarajan M, Mohammed B, and Kumar J (2010). Formulation of Microemulsion based vaginal gel *in-vitro* and *in-vivo* evaluation. Der Pharmacia Lettre, 2: 99-105.
- P. Sridhara Babu, M. Guravaiah, I. Hatti, K. Srikanth. Qualitative analysis of capsaicin from chillies and chilli powder by H.P.L.C method. Int. J. Curr. Res. Chem. Pharma. Sci. 2014, 1(6): 184-194.
- Patel J, Trivedi J, Chudhary S (2014). Formulation and evaluation of diacerein emulgel for psoriatic arthritis. Int J Pharm Res Bio-Sci, 3: 625-638.
- Prajapati MK., Patel MR., Patel KR., Patel NM. Emulgel: a novel Approach to topical drug delivery. International Journal Univ Pharm Bio Sci. 2013; 2(1): 134-148

- Rajesh Asija, Nitin Nama, Deepak Sharma Development and evaluation of novel Fluticasone Propionate Emulgel for topical drug delivery. Journal of Chemical and Pharmaceutical Research, 2015, 7(2): 772-780.
- Ricciotti, E. and G.A. Fitz Gerald, Prostaglandins and Inflammation. Arteriosclerosis, thrombosis, and vascular biology, 2011. 31(5): p. 986-1000.
- Sanjay, Jain BD, Padsalg A, Patel K, Mokale V. Formulation development and evaluation of fluconazole gel in various polymer bases. Asn J Pharm 2007; 1: 63- 68.
- SB Shirsand, MS Para, D Nagendrakumar, KM Kanani and D Keerthy. Formulation and evaluation of Ketoconazole niosomal gel drug delivery system. Int J Pharm Investig. 2012; 2(4); 201- 207.
- Snehal P. Mulye, Kiran A. Wadkar and Manish S. Kondawar Formulation development and evaluation of Indomethacin emulgel. Der Pharmacia Sinica, 2013, 4(5): 31-45
- Tushar L., Akhilesh D., Prabhakara P., Kamath J.V., 2012. Preformulation studies of controlled/sustained release formulations: an review. Int Res J Pharmacy, Vol. 3, Issue 5, pp. 95-99.
- V Singla; S Saini; AC Rana, Emulgel: a new platform for topical drug delivery. Int Pharma Sci., 2012, 2(3), 36-44.
- V. K. Singh, V. K. Mishra, J. K. Maurya, S. K. Singh, A. Mishra. Formulation and Evaluation of Cephalexin Monohydrate Reconstitutional Oral Suspension with Piperineand Their Antibacterial activity. World Journal of Pharmaceutical Research, 2014, 3(5), 821-831.