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FORMULATION DEVELOPMENT AND EVALUATION OF ETODOLAC EMULGEL WITH NATURAL PENETRATION ENHANCER

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Abstract*:* The purpose of this research was to prepare etodolac loaded emulsion for sustained release of drug and incorporate it in to topical gel delivery system to reduce the side effects by site specific targeting. The present work focused on the formulation of etodolac emulgel and the effect of natural permeation enhancers such as piperine and capsaicin. Etodolac emulgel was prepared by emulgel method by using various excipients such as polymers as carbopol-940, propylene glycol, tween20, and span20 and with penetration enhancers such as piperine and capsaicin. The prepared emulgel was evaluated for its properties Further the analysis of release mechanism was carried out by fitting the drug release data to various kinetic equations like zero order, first order, higuchi's and korssmeyer peppas equations and from the values so obtained, the best fit model were arrived at. From the above results formulation F4 was found to be best formulation for the topical release of etodolac that complied with all the parameters. It releases 73.79±0.98 % of drug 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 observed in the parameters evaluated like color, consistency, pH, rheological properties, skin permeability and drug release pattern. Therefore, it was concluded that etodolac emulgel formula could be very promising topical alternative for the conventional dosage form provide sustained and prolonged delivery of drug.

Key words: Etodolac, Emulgel, Piperine, Capsaicin, Formulation, Evaluation

Introduction: The objective of every drug delivery system (DDS) is to give a therapeutic quantity of drug to the appropriate site in the body to punctually attain and then uphold the preferred drug concentration [1, 2]. The route of administration is a useful brunt on the therapeutic outcome of a drug [3]. Most of these DDS are makeup of polymer, which contain the drug in the form of a dispersion of the solid drug particles either in a solid or in liquid medium [4]. Topical drug delivery systems allow localized administration of the active molecules/therapeutic agents wherever in the body through skin, vaginal, ophthalmic and rectal routes [5]. Topical formulations include an extensive diversity of formulations intended for cosmetic or dermatological application, to fit as well as diseased skin. These formulations range in physicochemical nature from solid through semisolid to liquid [6]. Therapeutic agents are infrequently managed alone, but rather as part of a formulation, in permutation with one or more non-medicated ingredients/excipients that serve diverse and particular pharmaceutical function [7].

For centuries, topical application of medications has been one of the most utilized routes for the treatment of localized skin diseases [8]. To be effective, drugs must reach an intended site in the body, at an effective concentration, and for an appropriate length of time. Currently, a vast majority of drugs are administered either orally or parenterally, even when the affected or diseased tissue-site(s) are topical ones. There are

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numerous drugs for which these forms of administration are not well-suited. For instance, oral administration of certain drugs may result in irritation of the gastro-intestinal tract and/or undesirable rapid first-pass metabolism [9]. First-pass metabolism, which refers to the chemical breakdown of compounds in the liver and gastro intestinal tract, can consequence in a significant decreasing in the quantity of drug reaching its intended site of activity in the body [10]. In some cases, liver damage may occur due to the toxicities associated with the breakdown of a particular drug. Systemic (oral/parenteral) administration leads to the exposure of drug to multiple naive tissues and organs (which are otherwise not being exposed) inducing unwanted and sometimes intolerable effects. Alternatively, oral delivery is fraught with several deficiencies like poor bioavailability (which requires higher dose level) and difficulty in sustaining the action, the parenteral administration on account of pain on pricking. Furthermore, such routes of administration are not convincing in case of afflictions on the external surface of the body such as skin [11, 12].

In the above background, the delivery of the drugs through topical administration has fetched a great attention in recent times. Science, with the evolving techniques and greater understanding are now able to address the relevant issues in making this form of therapy more useful. This may be either for the topically located problems or for using the skin (dermal delivery) as potential portal for systemic delivery (transdermal delivery) of drugs [13, 14]. Etodolac, a preferential COX-2 inhibitor, approved by US-FDA in 1996 is reported to be well tolerated in the patients with OA. It is frequently prescribed for the management of MSD by oral route of administration. The molecule is considered to have an edge over other NSAIDs like diclofenac, ibuprofen, aspirin and acetaminophen because of its established efficacy and safety profile. The key mechanism of its action is COX-inhibition along with obstruction of leukotriene and neutrophil activation. The key delivery-specific issues in topical delivery pertain to skin-penetration, dermal-retention and targets-interactions which otherwise are difficult to achieve in the frame of traditional excipients and approaches. For this reason, it is imperative to seek novelty in the design of vehicle with reverence to its construction and components.

Penetration enhancers support in the permeation of the preferred drug (penetrant) during the skin by lowering the impermeability of the skin. Some properties which are desired in permeation enhancers are the must be pharmacologically nonirritating, nontoxic, nonallergic, inert, compatible with drugs and excipients, tasteless, colorless, odorless, and inexpensive and also have superior solvent properties. But so far no topical formulation of etodolac is available for application with alkaloidal penetration enhancer. The major objectives include enhanced dermal penetration and skin deposition of etodolac leading to the improved pharmacological activity under favorable bio ambience without affecting the surrounding naive cells of the skin so we develop etodolac emulgel with alkaloidal penetration enhancer. To formulate an enhanced penetration rate emulgel for pain, reduced swelling and also used in arthritis which meet the requirements of system would allow easy administration into the pocket with minimal pain and discomfort, release the therapeutic agent at different levels over the required period of time and free from undesirable side effects.

Material and Methods

Material

All the chemicals used in this study were obtained from Hi Media Laboratories Pvt. Ltd. (Mumbai, India), Sigma-Aldrich Chemical Co. (Milwaukee, WI, USA), SD Fine-Chem. Ltd. (Mumbai, India) and SRL Pvt. Ltd. (Mumbai, India).All the chemicals and solvent used in this study were of analytical grade.

Methods

Extraction of piperine

Take 150 ml of 95% ethanol in round bottom flask and 5-10 boiling chips added. Take 15 gm of black pepper powder in the soxhlet apparatus and heat the reflux for 2-2.5 hours. Then the extracted mixture of round bottom flask was filtered by using suction pump. Then concentrate the filtered solution to a volume of 15-20 ml by simple distillation. Took the concentrated pepper extract in 125 ml of Erlenmayer flask and add the 10 ml of 10% solution of KOH and heated. The refluxing mixture was diluted with addition of water till the precipitation formation stopped. A brownish yellow precipitate was formed. The precipitate mixture is allowed to stand overnight. The resulted extracts were collected by filtering the precipitate by suction pump and then re-crystallized by 10-20 ml of acetone. A yellowish white crystal of piperine was obtained [15].

Extraction of capsaicin

Take 250ml of 95% ethanol in round bottom flask and 5-10 boiling chips added. Take 20gm of chilli powder in

soxhlet apparatus and heat the reflux for 2-2.5 hours. Then the extracted mixture of round bottom flask was filtered by using suction pump. Then concentrated the filtered solution to a volume of 15-20 ml by simple distillation. Took the concentrated extract of chili(capsaicin) dissolve in alcohol solution, heating and uniformly stirring, adding a mixed enzyme of lipase and cellulase into the capsacin alcohol solution and performing heat-preservation strring, adding a ferric chloride solution into a mixed solution heating uniformly stirring and separating out a light phase, concentrating and drying obtained purified capsaicin crystals [16].

Preparation of emulsion phases

The oily phase of emulsion was prepared by dissolving span-20 in light liquid paraffin with required quantity of Etodolac in ethanol. Piperine and capsaicin was added to it as a permeation enhancer. Aqueous phase was prepared by dissolving tween-20 in purified water. Methyl paraben was dissolved in propylene glycol and mixed with aqueous phase.

Preparation of gel

Accurately weighed quantity of carbopol-934 was taken in a previously dried beaker and 10 ml of distilled water was added to it. It was mixed well using mechanical shaker with constant stirring. More distilled water was added to it to maintain the consistency of the gel. The pH of the formulation was adjusted to 6.0 to 7.0 using triethanolamine.

Formulation of emulgel

Both the oily and aqueous phases were separately heated to 70^0C to 80^0C, than mixed with the continuous stirring and allowed to cool to room temperature. The obtained emulsion was mixed with the gel in 1:1 ratio with gentle stirring to obtain the Fluticasone propionate emulgel formulation [17, 18].

Table 1: Composition of Etodolac Emulgel Formulation (%w/w)

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9
Etodolac	1	1	1	1	1	1	1	1	1
Piperine	0.5	1	1.5	-	-	-	0.25	0.5	0.75
Capsaicin	-	-	-	0.5	1	1.5	0.25	0.5	0.75
Tween 20	0.5	1.0	1.5	0.5	1.0	1.5	0.5	1.0	1.5
Span 20	0.5	1.0	1.5	0.5	1.0	1.5	0.5	1.0	1.5
Methyl paraben	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
Light liquid paraffin	7	7	7	7	7	7	7	7	7
Propylene glycol	5	5	5	5	5	5	5	5	5
Purified water	qs	qs	qs	qs	qs	qs	qs	qs	qs

Evaluation of Emulgel

Physical characteristic: The prepared emulgel formulations were inspected visually for their pH, colour, homogeneity, consistency, grittiness, texture and phase separation.

Determination of pH: The pH of emulgel formulations was determined by digital pH meter. One gram of gel was dissolved in 25 ml of distilled water and the electrode was then dipped in to gel formulation for 30 min until constant reading obtained, and constant reading was noted. The measurement of pH of each formulation was done in triplicate and average values were calculated [19].

Washability: Formulations were applied on the skin and then ease and extent of washing with water were checked manually.

Extrudability study: The emulgel formulations were filled into collapsible metal tubes or aluminium collapsible tubes. The tubes were pressed to extrude the material and the extrudability of the formulation was checked [20].

Spreadability: Two glass slides of standard dimensions (6×2) were selected. The emulgel formulation whose spreadability had to be determined was placed over one of the slides. The second slide was placed over the slide in such a way that the formulation was sandwiched between them across a length of 6 cms along the slide.

100 grams of weight was placed up on the upper slide so that the emulgel formulation between the two slides was traced uniformly to form a thin layer. The weight was removed and the excess of the emulgel formulation adhering to the slides was scrapped off. The lower slide was fixed on the board of the apparatus and one end of the upper slide was tied to a string to which 20 gram load could be applied with the help of a simple pulley. The time taken for the upper slide to travel the distance of 6 cms and separate away from lower slide under the direction of the weight was noted. The experiment was repeated and the average of 6 such determinations was calculated for each emulgel formulation [21, 22].

$$\text{Spreadability} = \frac{m.l}{t}$$

Where, S=Spreadability (gcm/sec)
m = weight tied to the upper slide (20 grams)
l= length of glass slide (6cms).
t = time taken is seconds.

Viscosity: The measurement of viscosity of the prepared emulgel was done using Brookfield digital Viscometer. The viscosity was measured using spindle no. 6 at 10 rpm and 25^{0}C. The sufficient quantity of gel was filled in appropriate wide mouth container. The emulgel was filled in the wide mouth container in such way that it should sufficiently allow to dip the spindle of the viscometer. Samples of the emulgel were allowed to settle over 30 min at the constant temperature (25 ±/1^{0}C) before the measurements [23].

Drug content study: Drug content study was done to determine the amount of the drug present in the certain quantity of the formulation. Took 1 g of the formulation into 10 ml volumetric flask added 1 ml methanol in it and shake well and make up the volume with PBS pH 7.4. The Volumetric flask was kept for 2 hr and shaken well in a shaker to mix it properly. The solution was passed through the filter paper and filtered the mixer then measured absorbance by using spectrophotometer at 274 nm. [24]

Drug Content = (Conc. × Dilution Factor × Vol. taken) × Conversion Factor

In-vitro Drug release study: The in vitro drug release studies of the emulgel were carried out on Diffusion cell using egg membrane. This was clamped carefully to one end of the hollow glass tube of dialysis cell. Emulgel (1gm) was applied on to the surface of egg membrane dialysis membrane. The receptor chamber was filled with freshly prepared PBS (pH 7.4) solution to solubilise the drug. The receptor chamber was stirred by magnetic stirrer. The samples (1ml aliquots) were collected at suitable time interval sample were analyzed for drug content by UV visible spectrophotometer at 274nm after appropriate dilutions. Cumulative corrections were made to obtain the total amount of drug release at each time interval. The cumulative amount of drug release across the egg membrane was determined as a function of time. The cumulative % drug release was calculated using standard calibration curve [24].

Results and Discussion: Emulgel formulations were white viscous creamy preparation with a smooth homogeneous texture and glossy appearance. Results have been discussed in Table 1. The pH of the emulgel formulations was in the range of 6.8 ± 0.1 to 6.0 ± 0.4, which lies in the normal pH range of the skin and would not produce any skin irritation. There was no significant change in pH values as a function of time for all formulations. The emulgel was rotated at 50 rpm for 10 min with spindle 07. The corresponding reading was noted. The viscosity of the emulgel was obtained. The viscosity of the formulations increases as concentration of polymer increases. Spreadability of the emulgel was decreases with the increases in the concentration of the polymer. The spreadability is very much important as show the behaviour of emulgel comes out from the tube. The gels were filled into collapsible tubes after formulating them. The extrudability of the formulation has been checked and the results were tabulated Table 2. Drug content study was done to determine the amount of the drug present in the certain quantity of the formulation. Formulated emulgel was estimated by spectrophotometrically at 274 nm. In-vitro drug release study: The release of etodolac from the emulgel was varied according to concentration of polymer. The release of the drugs from its emulsified gel formulation can be ranked in the following descending order: F4 > F2 > F5> F1> F3 >F6 > F8 > F7>F9. The progressive increase in the amount of drug diffusion through membrane from formulation attributed to gradual decrease in the concentration of polymer. It has been over and done with that, if we raise the concentration of polymer, the diffusion of drug through the membrane also decreases. The drug content of the formulated emulgel was estimated by spectrophotometrically at 274 nm. The results were within the official limits and the

cumulative % drug release profile of all the formulation batches has been shown in Table 3.

Table 2: Physical parameter of formulation batches

Formulation	Colour	Homogeneity	Consistency	Phase separation
F1	White	Excellent	Excellent	None
F2	White	Excellent	Excellent	None
F3	White	Excellent	Excellent	None
F4	White	Excellent	Excellent	None
F5	White	Excellent	Excellent	None
F6	White	Excellent	Excellent	None
F7	White	Excellent	Excellent	None
F8	White	Excellent	Excellent	None
F9	White	Excellent	Excellent	None

Table 3: Results of evaluation Different Formulations F1-F9 (Mean±S.D.)

Formulation	pH	Viscosity (cps)	Spreadability (gcm/sec)	Extrudability	Washability	Drug Content (% W/W)
F1	6.80± 0.1	4450	14.56±0.21	++	+++	97.72±0.15
F2	6.72± 0.3	4565	13.25±0.36	+	+++	99.12±0.3
F3	6.22± 0.2	4632	16.65±0.56	+++	+++	99.70±0.26
F4	6.65± 0.3	4755	15.45±0.45	+++	+++	99.62±0.36
F5	6.87± 0.5	4898	15.65±0.58	++	++	98.76±0.4
F6	6.45± 0.4	4950	16.45±0.32	++	++	98.45±0.35
F7	6.31± 0.6	4990	14.45±0.12	++	++	99.43±0.5
F8	6.65± 0.6	4865	10.25±0.32	++	++	98.78±0.20
F9	6.02± 0.4	4850	14.45±0.12	+++	+++	99.54±0.47

Excellent: +++, Good: ++, Average: +

Table 4: In Vitro Cumulative % Drug Release Different Formulation F1-F9

Time in (Hrs)	Cumulative % Drug Release (% w/w)								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	**0**	**0**	**0**	0	**0**	**0**	**0**	**0**	0
1	8.43±0.14	10.71±0.10	13.21±0.03	4.15±0.01	4.92±0.09	7.36±0.12	3.67±0.05	9.93±0.07	6.23±0.11
2	16.09±0.27	21.66±0.52	29.43±0.08	25.35±0.36	14.75±2.63	14.07±0.08	13.24±0.45	21.46±0.11	14.46±0.09
3	25.38±1.04	26.47±0.34	36.12±0.23	31.91±0.47	23.37±0.33	22.87±1.23	16.34±0.13	26.12±1.34	20.02±0.01
4	31.53±0.45	33.07±1.23	42.27±0.12	38.30±0.89	29.5±1.96	29.45±0.24	21.49±0.26	33.08±1.23	27.56±0.23
5	38.59±0.17	41.75±1.34	51.19±0.24	44.73±0.11	34.37±0.25	33.63±0.17	27.37±0.23	38.98±0.43	32.22±0.52
6	43.52±0.31	47.97±0.19	56.64±0.23	52.62±0.11	40.56±0.28	38.64±2.10	34.93±0.23	43.16±0.31	38.85±0.14
7	47.94±0.34	54.79±0.26	60.32±0.23	54.48±0.69	47.37±1.50	46.32±0.13	41.29±0.32	47.59±0.23	45.19±1.31
8	65.38±0.23	70.11±1.29	62.78±2.28	73.79±0.98	68.90±1.23	59.97±2.15	52.67±0.14	56.12±0.27	49.08±0.42

Table 5: Regression co-efficient (R2) values of kinetic models for formulation F4

Formulation	*Regression* Coefficient	Zero order	First order	Higuchi	Peppas
F4	r^2	0.963	0.943	0.991	0.990

Conclusion: The present work focused on the formulation of etodolac emulgel and the effect of natural permeation enhancers such as piperine and capsaicin. Etodolac emulgel was prepared by emulgel method by using various excipients such as polymers as carbopol-940, propylene glycol, tween20, and span20 and with penetration enhancers such as piperine and capsaicin. The prepared emulgel was evaluated for its properties Further the analysis of release mechanism was carried out by fitting the drug release data to various kinetic equations like zero order, first order, higuchi's and korssmeyer peppas equations and from the values so obtained, the best fit model were arrived at. From the above results formulation F4 was found to be best formulation for the topical release of etodolac that complied with all the parameters. It releases 73.79±0.98 % of drug 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 observed in the parameters evaluated like color, consistency, pH, rheological properties, skin permeability and drug release pattern. Therefore, it was concluded that etodolac emulgel formula could be very promising topical alternative for the conventional dosage form provide sustained and prolonged delivery of drug.

References

1. Alfonso R.Gennaro, Remington: The Science & Practice of Pharmacy, 17th edition, Mack Publishing Company; 1985 Chapter No. 11 Pharmaceuitical and Medicinal agents, P. 1644-1661.
2. Chein YW. Novel drug delivery systems: Fundamentals, development, concepts and biomedical application. Marcel Dekker, New York, 1981; P. 139-217.
3. Robinson RJ, Lee VH. Controlled Drug Delivery: Fundamental & Application. 2nd edition, Marcel Dekker, New York; 1987: Chapter-1"Influence of drug properties and routes of drug administration on the design of sustained and controlled release systems" P 4-61.
4. Chein YW, Novel Drug Delivery delivery system 2nd edition, 2009, USA: "Transdermal drug delivery system" P 301-380.
5. Walters KA. Dermatological and transdermal formulation. Florida CRC Press. 2002 ;(403): 323-327.
6. 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
7. Rashmi M., Sharma S. Topical preparations are used for the localized effects at the site of their application by virtue of drug penetration into the underlying layers of skin or mucous membranes. Pharmaceutical reviews 2008 ;(6):1
8. Tadicherla, S. and Berman, B. (2006). "Percutaneous dermal drug delivery for local pain control." Ther Clin Risk Manag. 2(1): 99-113.
9. Nino, M., Calabro, G. and Santoianni, P. (2010). "Topical delivery of active principles: The field of dermatological research." Dermatology Online Journal 16(1).
10. Bleier, B. S. (2010). "Novel Topical Therapeutics." Otolaryngologic Clinics of North America 43(3): 539-549.
11. Grayson, L. D. (1963). "Topical skin therapeutics: The active medication." Skin (Los Angeles) 210: 383-387.
12. Bouwstra, J. A., Honeywell-Nguyen, P. L., Gorris, G. S. and Ponec, M. (2003). "Structure of the skin barrier and its modulation by vesicular formulations." Progress in lipid research 42:1-36.
13. Vijay Kumar Singh, Vikash Kumar Mishra, Jayant Kumar Maurya, Sarvesh Kumar Singh, Ashutosh Mishra. Formulation and Evaluation of Cephalexin Monohydrate Reconstitutional Oral Suspension with Piperine and Their Antibacterial activity. World Journal of Pharmaceutical Research, 2014,3(5), 821-831.
14. 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.
15. M. I. Mohamed, Topical emulsion-gel composition comprising diclofenac sodium, *AAPS Journal*, 2004, 6(3), 1-6.
16. 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.
17. Jain A, Gautam SP, Gupta Y, Khambete H, Jain S. Development and characterization of ketoconazole emulgel for topical drug delivery. Der Pharmacia Sinica 2010; 1(3): 221-231.

18. Gupta GD, Gaud RS. Release rate of Nimesulide from different gellants. Ind J Pharm Sci 1999; 61: 229-234.
19. 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.
20. Gupta GD, Gaud RS. Release rate of Tenoxicam from Acrypol gel. The Indian Pharmacist 2005; 69-76.
21. Margaret N, Mutimer CR, Hill JA, Murray E. Modern ointment base technology comparative evaluation of bases. J American Pharm Association 1956; 4: 212-217.
22. Jain A, Deveda P, Vyas N, Chauhan J. Development of antifungal emulsion based gel for topical fungal infection(s). Int J Pharm Res Dev., 2011, 2(12), 18-22.
23. V Singla; S Saini; AC Rana, Emulgel: a new platform for topical drug delivery. Int Pharma Sci., 2012, 2(3), 36-44.
24. Snehal P. Mulye, Kiran A. Wadkar and Manish S. Kondawar. Formulation development and evaluation of Indomethacin emulgel Der Pharma Sin., 2013, 4(5), 31-45.