International Journal of Sciences & Applied Research

www.ijsar.in

Formulation development and evaluation of Aceclofenac loaded Emulgel

Preet N. Gokani[1]*, Dr. Mittal Maheshwary[2], Dr. Pragnesh Patani[3]

[1]A-One Pharmacy College, SNME Campus, Naroda-Dehgam Road, Ahmedabad.
[2]Asso.Proff. & Head of Department Pharmaceutics A-One Pharmacy College.
[3]Principal I/c & Head of Department Pharmacognocy A-One Pharmacy College.

Corresponding author: *Preet N. Gokani, A-One Pharmacy College, SNME Campus, Naroda-Dehgam Road, Ahmedabad.

Abstract

Emulgel is the most emerging and successful formulation to deliver hydrophobic drugs. When gels and emulsions are used in combined form, the dosage forms are referred as Emulgels. It imbibes the properties of both gel and emulsion which results in enhancing the solubility of the hydrophobic drug to make the drug more bioavailable and enhances the patient compliance as topical drug delivery dosage form. Aceclofenac is NSAID, derivative of diclofenac, used as analgesic and anti-inflammatory agent belongs to BCS class – II drug (low solubility and high permeability) is taken as a drug of choice to formulate as Emulgel. Less dose is sufficient to prepare as topical dosage form. Here, emulgels were prepared as 1% w/w formulation by using carbomer 934 and HPMC K4M separately as gelling agents. Linseed oil as penetration enhancer. Emulgels were prepared and evaluated for rheological properties, pH determination, drug release profiles. The present study reveals that the formulation using carbomer 934 shown better release profile than HPMC K4M which depicts, carbomer 934 is the better choice of polymer to prepare aceclofenac emulgel.

Keywords: Aceclofenac, Topical Drug Delivery System, Emulgel

Introduction

Over the last decades the treatment of illness has been accomplished by administering drug to human body via various routes namely oral, sublingual, rectal, parental etc. The topical drug delivery system is generally used where these systems of drug administration fails or in local skin infection like fungal infection. Delivery of drugs to the skin is an effective and targeted therapy for local dermatological disorders. This route of drug delivery has gained popularity because it avoids first pass effects, gastrointestinal irritation, and metabolic degradation associated with oral administration. Due to the presystemic metabolism only 25-45% of the orally administered dose reaches the blood circulation. In order to bypass these disadvantages the gel formulations have been proposed as topical application. Topical drug delivery can be defined as the application of a drug containing formulation to the skin to directly to treat cutaneous

formulation disorder Dermatological products applied to skin are diverse in formulation & range in consistency from liquid to powder but the most popular products are semisolid preparations includes ointments, creames, pastes, gels.

Topical gel formulations provide a suitable delivery system for drugs because they are less greasy and can be easily removed from the skin. Precutanous absorption of drugs from topical formulation involves the release of the drug from the formulation and permeation through skin to reach the target tissue. The release of the drug from topical preparations depends on the physicochemical properties of the vehicle and the drug employed. In order to enhance drug and skin permeation, methods such as the selection of suitable vehicle, co-administration of a chemical enhancer have been studied.

Use of topical agents requires an appreciation of the factors that influence precutanous absorption. Molecules can penetrate the skin by three routes, through intact stratum corneum, through sweat glands, or through the sebaceous follicle. The surface of the stratum corneum presents more than 99% of the total skin surface available for precutanous drug absorption. Passage through this outermost layer is the rate –limiting step for precutanous absorption. The major steps involved in precutanous absorption include the establishment of a concentration gradient ,which provides the driving force for drug movement across the skin ,release of drug from the vehicle (penetration co-efficient);and drug diffusion across the layers of the skin(diffusion co-efficient). Preferable characteristic of topical drugs include low molecular mass (400 Daltons) with adequate solubility in oil & water, and have high partition co-efficient for the topical formulation. Gels are a relatively newer class of dosage form created by entrapment of large amounts of aqueous or hydro alcoholic liquid in a network of colloidal solid particles.gel formulations generally provide faster drug release compared with ointments and creams. Major drawback of topical dosage form diffusion of drug in the delivery of hydrophobic drugs, and permeation through stratum corneum is for hydrophilic drugs. Therefore, to overcome this limitation emulgels are prepared.

TOPICAL DELIVERY INCLUDES TWO BASIC TYPES OF PRODUCTS

1. External topical that are spread, sprayed or otherwise dispersed on to cutaneous tissues to cover the affected area.
2. Internal topical that are applied to the mucous membrane orally, vaginally or on a rectal tissues for local activity.

A. Factors Affecting Topical Absorption of Drug Physiological Factors:

- Skin thickness.
- Lipid content.
- Density of hair follicles.
- Density of sweat glands.
- Skin pH.
- Blood flow.
- Hydration of skin.
- Inflammation of skin

Physiochemical Factors:

- Partition coefficient.
- Molecular weight (<400 dalton).
- Degree of ionization (only unionized drugs gets absorbed well).
- Effect of vehicles.

B. Advantages of Topical Drug Delivery System

- Avoidance of first pass metabolism.
- Avoidance of gastrointestinal incompatibility.
- More selective to a specific site.
- Improve patient compliance.
- Suitability for self medication.

- Providing utilization of drug with short biological half life and narrow therapeutic window.
- Ability to easily terminate medication when needed.

C. Disadvantages of Topical Drug Delivery System

- Skin irritation on contact dermatitis.
- Possibility of allergenic reactions.
- Poor permeability of some drug through skin.
- Drug of large particle size are not easy to absorb through the skin.

Physiology of skin

Most of the topical preparations are meant to be applied to the skin. The skin of an average adult body covers a surface area approximately 2m and receives about one third of the blood circulating through the body. An average human skin surface is known to contain, on the average 4070 hair follicles and 200-300 sweat ducts on every square centimeter of the skin as shown in Fig.1. The pH of the skin varies from 4-5.5. Sweat and fatty acid secreted from sebum influence the pH of the skin surface. The skin can be considered to have four distinct layers of tissue.

1. Non-Viable Epidermis:

Stratum corneum is the outer most layer of skin, which is the actual physical barrier to most substance that comes in contact with the skin. The stratum corneum is 10 to 20 cell layer thick over most of the body. Each cell is a flat, plate like structure 34-44μm long, 25-36 μm wide,0.5 to 0.20μm thick with surface area of 750 to 1200μm stocked up to each other in brick like fashion. Stratum corneum consists of lipid (5-15%) including phospholipids, glycosphingo lipid, cholesterol sulfate and neutral lipid, protein (75-85%) which is mainly keratin.

2. Viable Epidermis:

This layer of the skin resides between the stratum corneum and the dermis and has a thickness ranging from 50-10μm. The structures of the cells in the viable epidermis are physiochemical similar to other living tissues. Cells are held together by tonofibrils. The density of this region is not much different than water. The water content is about 90%.

3. Dermis:

Just beneath the viable epidermis is the dermis. It is a structural fibrin and very few cells are like it can be found histological in normal tissue. Dermis thickness ranges from 2000 to 3000 μm and consists of a matrix of loose connective tissue composed of fibrous protein embedded in an amorphous ground substance.

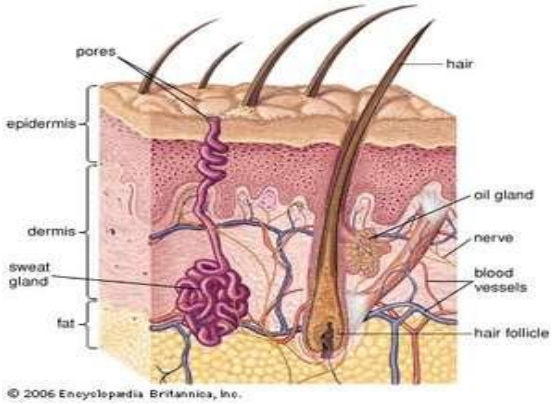


Fig. 1-Structure of the Human Skin

4. Subcutaneous Connective Tissue:

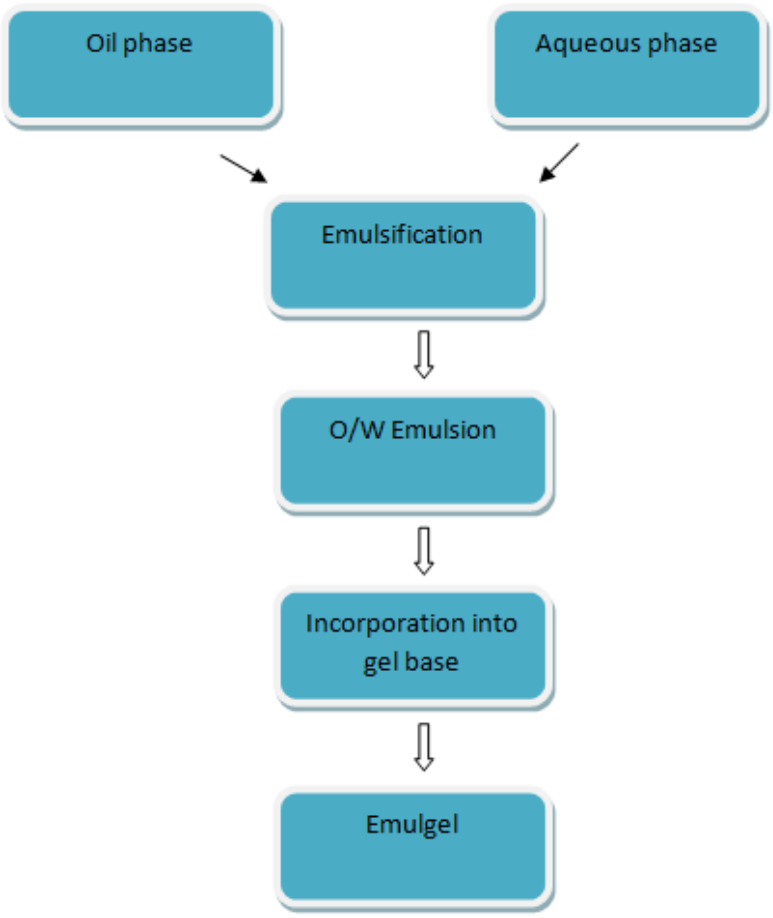
The subcutaneous tissue or hypodermis is not actually considered a true part of the structured connective tissue which is composed of loose textured, white, fibrous connective tissue containing blood and lymph vessels, secretary pores of the sweat gland and cutaneous nerves. Most investigators consider drug permeating through the skin enter the circulatory system before reaching the hypodermis, although the fatty tissue could serve as a depot of the drug.

Drug delivery across the skin

The epidermis is the most superficial layer of the skin and is composed of stratified keratinized squamous epithelium which varies in thickness in different parts of the body. It is thickest on with elastic fibers. The skin forms a relatively waterproof layer that protects the deeper and more delicate structures. Blood vessels are distributed profusely beneath the skin. Especially important is a continuous venous plexus that is supplied by inflow of blood from the skin capillaries. A unique aspect of dermatological pharmacology is the direct accessibility of the skin as a target organ for diagnosis and treatment. The skin acts as a two-way barrier to prevent absorption or loss of water and electrolytes.

Materials and method of Preparation

- Aceclofenac was obtained as the gift sample from the West-Coast Pharmaceuticals Ltd.- Ahmedabad. All the other chemicals used in the experiment were of the analytical grades.



- Formulations of Emulgel

Table 1: Different batches of Emulgel

Ingredients %w/w	Emulgel 100 gm. Bathes							
	F1	F2	F3	F4	F5	F6	F7	F8
Aceclofenac	1	1	1	1	1	1	1	1
Linseed oil	3	3	3	3	3	3	3	3
Menthol	5	5	5	5	5	5	5	5
Methyl Salicylate	10	10	10	10	10	10	10	10
Propylene Glycol	10	10	10	10	10	10	10	10
Methyl Paraben	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Propyl Paraben	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Tween 80	2	2	2	2	2	2	2	2
Carbomer 934	1	1	1	1	1	1	1	1
HPMC K4M				0.5	1	1.5		1
Ethyl Acetate	7	7	7	7	7	7	7	7
Distilled Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

- **Evaluation Parameters:**

1. Physical Appearance:

The prepared emulgels were inspected visually for clarity, colour, and presence of any particle. The test is important regarding patient compliance.

2. pH:

pH of the gel was determined using digital pH meter. About 1.0 gm of gel was stirred in distilled water till uniform suspension effected. The volume was made upto 50ml and pH of the solution was measured.

3. Spreadability:

It was determined by apparatus of a wooden block, which is attached to a pulley at one end. Spreading coefficient was measured on the basis of 'Slip' and 'Drag' characteristics of emulgels. A glass slide was fixed on the wooden block. An excess of emulgel (about 2 g) under study was placed on this ground slide. The emulgel preparation was then sandwiched between this slide and second glass slide having same dimension as that of the fixed ground slide. The second glass slide is provided with the hook. Weight of 500 mg was placed on the top of the two slides for 5 min to expel air and to provide a uniform film of the emulgel between the two slides. Measured quantity of weight was placed in the pan attached to the pulley with the help of hook. Time in seconds taken by two slides to slip off from emulgel and placed in between the slides under the direction of certain load. Lesser the time taken for separation of two slides, better the spreadability. It is calculated by using the following formula.

$S = M^* L / T$

Where, M = wt. tied to upper slide; L = length of glass slides; T = time taken to separate the slides

4. Extrudability Study:

For a good gel formulation, it should extrude easily from the container. In this test, sample is extruded from the tube by usual procedure. A closed collapsible tube containing gel was passed firmly at crimpened end. When the cap was removed, gel extrudes until pressure was dissipates. The time required to extrude 0.5 cm ribbon of gel with 500 gm weight was determined. The results for each formulation were recorded in seconds.[30]

5. Rheological Study:

The viscosity of the different emulgel formulation were determined at 37°C using a Brookfield viscometer DV III+ with spindle no. 4. The formulation whose viscosity was to be determined was added to the beaker spindle was lowered perpendicular into the centre of emulgel taking care does not touch bottom of the jar and rotated for 10 min and 100 rpm.

6. Drug content study:

1gm of gel was dissolved in small amount of ethanol in a 100ml flask and was shaken till it was completely dissolved and then volume was made up to 100ml by using ethanol. The solution was filtered through whatman filter paper. Further dilute 5ml to 50 ml with ethanol. The absorbance of the solution was measured at 275nm.

7. In-vitro drug release kinetics:

In-vitro drug release studies were carried out using Franz Diffusion cell. The formulation was applied on egg membrane which was sandwiched between donor and receptor compartment of Franz Diffusion cell. Phosphate buffer pH 7.2 + ethanol (80:20) were used as a dissolution media. The temperature of the cell was maintained at 37±0.5°C by kept in water bath. This whole assembly was kept on a magnetic stirrer and the solution was stirred continuously using a magnetic bead at 50 rpm. The samples (1.0ml) were withdrawn at suitable time interval and analyzed for drug content by UV visible spectrophotometer at 275 nm after appropriate dilutions.

Result and Discussion

1. Physical Appearance:

All the aceclofenac emulgels formulations were found to be homogenous and showed no clogging and lumps which indicate good texture of system. All formulation batches were found to be homogenous yellowish milky emulsions previously while emulgels were found to be whitish viscous creamy preparation.

2. pH:

The pH of all the formulations was ranging in between 6.1-6.5 which is comparable to the human skin pH which is around 5.5.

Table 2: pH of the formulations

Formulations	pH			Mean(n=3)
F1	6.3	6.5	6.0	6.2
F2	6.7	6.1	6.4	6.4
F3	6.1	6.3	5.9	6.1
F4	6.5	5.9	6.2	6.2
F5	6.4	6.7	6.1	6.4
F6	6.8	6.3	6.4	6.5
F7	6.6	6.1	6.3	6.3
F8	6.6	6.0	6.4	a.

3. Spreadability:

Emulgel is considered to be good if it takes minimum time to spread on the surface. Among the various gels studied F3 emulgel has better spreadability. The values of spreadability indicate that the gel is easily spreadable by small amount of shear.

Table 3: Spreadability of the Formulations

Formulations	Time (sec.)			Mean(n=3)
F1	12	13	15	13
F2	14	12	11	12
F3	10	11	13	11
F4	11	13	12	12
F5	16	14	15	15
F6	15	17	13	15
F7	13	16	15	14
F8	18	16	15	16

4. Extrudability Study:

The values of extrudability of different formulations were range in between 13-18 seconds it indicates that all the formulation were easily extruded out.

Table 4: Extrudability study of formulations

Formulations	Time (sec.)			Mean(n=3)
F1	14	18	17	16
F2	13	15	16	14
F3	13	12	15	13
F4	18	16	19	17
F5	15	19	18	17
F6	16	20	19	18
F7	18	17	21	18
F8	16	15	19	16

5. Rheological Study:

The viscosity of the formulations were studied at the 100 rpm of spindle no. 4 at 37^{o}C.

Table 5: Rheological study of formulations

Formulations	Viscosity (cPs)			Mean(n=3)
F1	1252	1089	1467	1269
F2	1029	1287	1445	1253
F3	955	1189	1076	1073
F4	1023	1187	1654	1288
F5	1286	1837	1342	1488
F6	1314	1764	1456	1511
F7	1048	1421	983	1150
F8	1363	1678	1710	1583

6. Drug diffusion study:

Different formulations were taken at the various time intervals and were measured by using UV Shimadzu 1800 at 275nm. wavelength.

Table 6: % Drug diffusion of formulations

Formulations	% Drug diffusion
F1	94.3
F2	87.6
F3	96.9
F4	93.3
F5	97.4
F6	98.5
F7	95.1
F8	91.3

7. In-vitro drug release kinetics:

Drug release of the different formulations were checked at the interval of 1 hour upto 12 hours it was found better in the F3 and F6 formulations.

Table 7: Drug release kinetics of different formulations

Time (hrs.)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1	5.17	4.10	5.56	5.76	3.94	8.80	4.10	5.18
2	12.02	7.25	13.61	7.51	6.15	16.51	7.25	7.93
3	16.54	10.93	21.25	11.05	9.37	29.72	10.93	12.45
4	25.16	12.28	32.13	16.54	11.20	38.64	12.28	17.62
5	33.47	23.68	39.58	25.93	22.46	47.38	23.68	26.01
6	41.31	28.41	46.40	30.24	25.34	55.13	28.41	32.85
7	49.67	33.06	51.79	38.85	29.81	63.02	33.06	42.65
8	58.46	37.12	62.83	40.69	34.65	70.61	37.12	46.42
9	60.02	42.62	68.32	45.65	40.65	83.45	42.62	49.83
10	68.32	49.53	74.82	52.25	46.74	77.54	49.53	52.64
11	74.60	53.62	81.25	55.48	50.15	90.05	53.62	57.45
12	76.77	60.31	89.53	63.42	58.09	98.86	60.31	62.06

Discussion

The future of pharmaceutical products will be rush up with topical delivery products because of drawbacks in oral, parenteral and other routes and more patient compliance. Loading of hydrophobic drug in hydrophilic gel matrix was found a solution by emulgel. Emulgel possess excellent bioadhesion, viscosity and long term stability which will increase compliance. In this study emulgels

were prepared by using two different gel forming polymers in which the gel formulation with Carbomer 934 showed better clarity and stability for longer period of time.

Conclusion

In this study emulgels were prepared by using two different gel forming polymers in which the gel formulation with Carbomer 934 showed better clarity and stability for longer period of time. In the study it was observed that the concentration of tween80 and linseed oil have shown effect on viscosity, spreadability and in-vitro drug permeability.

In terms of pH the observed value of all the formulations were comparable to human skin pH. All the formulation were found to be easily spreadable. In drug permeation study and drug release data showed that F6 formulation showed better drug release data compared to other formulations. So it is considered as the optimized batch. Hence, Aceclofenac emulgel was successfully prepared and evaluated.

References

1. Rachit Khullar, emulgels: a surrogate approach for topically used hydrophobic drugs- International journal of pharmacy and biological sciences- 2011, 117-128
2. Kaisar Raza, topical delivery of aceclofenac: challenges and promises of novel drug delivery system- Biomed research journal – 2014, 406731
3. Ashara Kalpesh C - Emulgel: a no refusable formulation to improve solubility, penetration and percentage of aceclofenac release for suppressing PGE_2 synthesis- British Biomedical Bulletin- 2014, 2347-5447**.**
4. Debjit Bhowmik - The pharma innovation recent advances in novel topical drug delivery system- The pharma journal- 2012, 2277-7965.
5. Ashni Verma - Topical gels as drug delivery system: A review-International journal of pharma sceinces and research- 2013, (374-382)
6. Rachit Khullar - Emulgels: A surrogate approach for topically used hydrophobic drugs- International journal of pharmacy and biosciences- 2012, (117-12)
7. K.P.Mohammed Haneefa - Emulgel: An advanced review- Journal of pharmaceutical sciences and research – 2013, (254-258)
8. A.S.Panwar - Emulgel: A Review, Asian journal of pharmacy and life sciences, , (2011).
9. Aceclofenac- https://www.drugbank.ca/drugs/DB06736
10. Noh K, absolute bioavailability and metabolism of aceclofenac in rats- Arch pharm- 2015, 68-72.
11. Burkhard Hinz, Aceclofenac spares cox-1 as a result of limited but sustained biotransformation to diclofenac- clinical pharmacology& therapeutics- 2003, 222-235.
12. Dr. Mansij Biswas, Topical route of administartion and dosage forms, slide share.
13. N.S.Chandrasekhar, Physicochemical and pharamcokinetic parameter in drug selection and loading for transdermal drug delivery- Indian journal of pharmaceutical science-2008, 94-96.
14. Shakeel F Ramadan, Solubilityand dissolution improvement of aceclofenac using different nanocarriers- J bioeuivalance availab -2009, 039-043.
15. Drug Index- www.drugsupdate.com/genric/view/5/Aceclofenac
16. Drug Update- www.drugsupdate.com/brand/showavailablebrands/5/17
17. Aceclofenac – 2018 https://en.m.wikipedia.org/wiki/acecloofenac
18. CAS registry number https://en.m.wikipedia.org/wiki/CAS_Registry_Number

19. Arun Gokul T.S, Formulation and Optimization of Aceclofenac gel- Research in Pharmacy- 2013, 14-22.
20. Pottalaswathi, Formulation and evaluation of aceclofenac topical emulgel- IJAPSIRD, 2015(0052-0057).
21. Snehal P. Mulye, Formulation development and evaluation of Indomethacin emulgel- Pelagia Research Library, 2013,4(5):31-45
22. Rajesh Katara, Aceclofenac oil Drops: Characterization and evaluation against ocular inflammation- Pharmaceutical Development and Technology,2017-1097-9867.
23. Aijaz A. Sheikh, Formulation development and characterization of Aceclofenac gel conatining linseed oil and ginger oleoresin-IJPTR, 2011-(1448-1453).
24. P C Sathya Keerthi Pani, Emulgel: A novel for enhancing topical delivery of Aceclofenac- Inventi Rapid: NDDS Vol. 2015-(0976-3791).