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FORMULATION AND EVALUATION OF ACECLOFENAC TOPICAL EMULGELS

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ABSTRACT

Aceclofenac is a new non-steroidal anti-inflammatory drug (NSAIDs) having a remarkable analgesic, anti-inflammatory and anti-pyretic potential. Chemically it is named as (2-[(2,6- dichlorophenyl) amine] or phenylacetoxya acetic acid. So, this research was based on designing and formulation of topical aceclofenac emulgel with different and suitable gelling agents with different ratio of mixing and evaluation of same by following standard parameters. Firstly, preformulation studies were done to make sure the raw materials are of quality grade. The different emulgels were formulated as Aceclofenac (API), API + Span 20, API + Tween 20, API + Carbopol 934, API + HPMC K4 M, API + Liq. Paraffin, API + Propylene Glycol, API + Menthol and API + Methyl Paraben. The emulgels were evaluated for various parameters such as physical tests, rheological properties, estimation of pH, skin irritation test, in-vitro drug release and swelling index. The different formulations of Emulgels were evaluated for their rheological properties. Formulation no. 1, 2 and 3 were analyzed at RPM 0.2. At shear stress of 165.8 for F1 demonstrated the viscosity of 13950. For F2 at shear stress 170.6 the viscosity was noted as 15526. At last, for F3 at shear stress of 170.6 the viscosity was found as 14526. The in-vitro drug release study was recorded from 0.5 hr to 8 hrs. The amount of drug was found to be 1.32mg, 1.31mg and 1.31mg in 1 gm of Emulgel formulation no. 1, 2 and 3. This research comes under the New Drug Delivery System (NDDS) that enhances the new approach in frequent dermal delivery of loaded Aceclofenac topical emulgel.

KEYWORDS: Aceclofenac, Emulgel, NDDS, Topical.

INTRODUCTION

Aceclofenac is a new non-steroidal anti-inflammatory drug (NSAIDs) having a remarkable analgesic, anti-inflammatory and anti-pyretic potential. Chemically it is named as (2-[(2,6- dichlorophenyl) amine] or phenylacetoxya acetic acid (Grau et al. 1991).

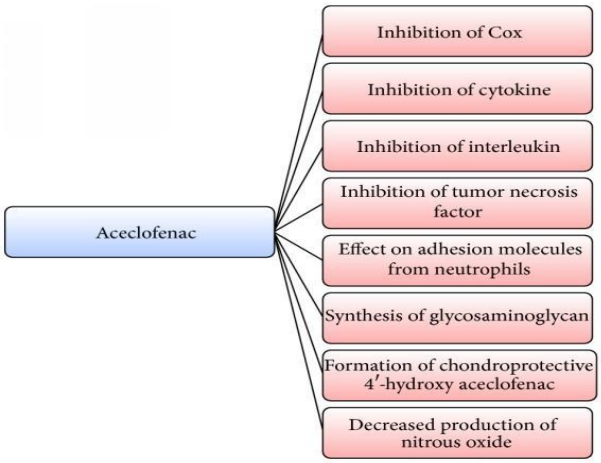

Fig. 1: Impacts of Aceclofenac on body system (Raza et al. 2014).

Aceclofenac (100 mg) displays a supported barricade of COX-2 in-vivo however shows just a minor restraint of COX-1, contrasted and 75 mg diclofenac. Some controlled clinical preliminaries have shown that aceclofenac is viable and very much endured in patients with Osteoarthritis, rheumatoid joint pain (RA), and spondylitis (anky-losing). Aceclofenac is quite possibly the most ordinarily utilized NSAIDs all through the Spain (Gualda et al. 2007). Both Etoricoxib and Aceclofenac are similarly powerful in diminishing the torment force and working on the useful capacity in intense low back torment. Notwithstanding, cost-viability examination demonstrated Etoricoxib to be a more financially savvy intercession when contrasted and Aceclofenac. Henceforth, both Etoricoxib and Aceclofenac are powerful analgesics in intense low back torment, in any case Etoricoxib was assessed to be a savvy mediation (Jagannathan et al. 2020).

The structure of aceclofenac is depicted below-

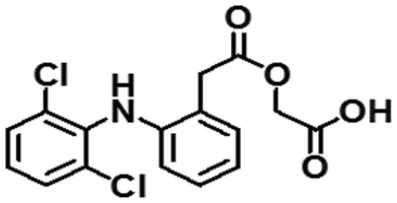

Fig. 2: Structure of Aceclofenac (Koly et al. 2015).

Torment is an abstract involvement in two correlative angles: one is a restricted sensation in a specific body part; the other is an upsetting nature of changing seriousness regularly connected with practices coordinated at mitigating or ending the experience (Yam et al. 2018; Pain and Disabilities, National Academies Press, 1987).

Aceclofenac is a favored COX-2 inhibitor having calming and pain-relieving possibilities. Aceclofenac additionally focuses on the biosynthesis of glycosaminoglycan and along these lines intervenes chondroprotective impacts. It shows more regular gastrointestinal results like dyspepsia, stomach-throb and queasiness (Jagannathan et al. 2020).

Etoricoxib (another NSAID) is a COX-2 specific inhibitor having calming, pain relieving and antineoplastic possibilities. It shows less continuous frequency of gastrointestinal results, however expanded cardiovascular unfavorable occasions (Jagannathan et al. 2020).

It's anything but a professional medication of diclofenac and decayed effectively under the hydrolytic medium like impartial, acidic and basic and furthermore on openness to light. The compound is steady to oxidative pressure, temperature, and photolytic stress, in solid state (Bushra et al. 2013).

Importance of Emulgels (Yadav et al. 2017)

- Avoidance of pre-systemic metabolism
- Avoidance of g.i.t. incompatibility
- Site specific
- Better patient compliance
- Self-administration suitability
- Better stability
- Controlled release

Emulgels are boon for the dermatological advances in drugs and cosmetic science. Polyethylene glycol and isopropyl alcohol increase the permeation and absorption through percutaneous layer (Verma et al. 2017).

Structure of Emulgel (Sreevidya, 2019)

The following figure demonstrates the physical appearance or structure of the emulgels. It has been observed in the reference with the skin.

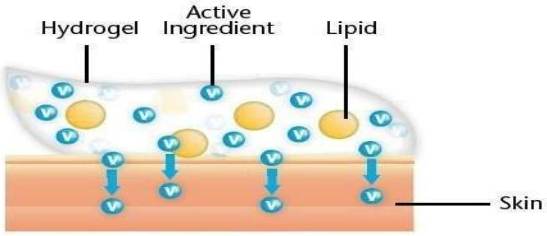

Fig. 3: 2Structure of emulgel.

Pravallika & Priyanka (2019) were figured and considered aceclofenac effective emulgel. They utilized diverse gelling specialists as carbopol 934, Hydroxyl propyl methyl cellulose, Sodium carboxyl methyl cellulose and Sodium alginate.

On the basis of above literature survey, I found that emulgel of aceclofenac can be developed with different gelling agent to facilitate dissolution, bioavailability and stability of the topical emulgel formulation.

So, this research focuses on designing and formulation of topical aceclofenac emulgel with different and suitable gelling agents with different ratio of mixing and evaluation of same by following standard parameters.

MATERIALS AND METHODS

1. Experimental Requirements

The following are the Equipment, Instrument, and Materials that were used for the formulation and evaluation of Drug-

- Aceclofenac, carbopol 934, Tween 80, Span 80, Propylene glycol, ethanol, clove oil, Methyl paraben.
- Digital balance, magnetic stirrer, Spectrophotometer, compound microscope, Dissolution test apparatus, pH meter.

2. Preformulation Studies

Preformulation studies are performed for the improvement of Emulgel before the initiation of plan advancement, and the significant objective of the investigation is to create or foster steady, safe, and restoratively powerful and effectual dose frames that are essentially identified with the portrayal of the physicochemical properties of the medication substance. The major aim of the pre-formulation studies before product development are:

- To establish the important physicochemical nature & characteristics of the drug.
- For the determination of drug compatibility with different excipients used in the formulation.

3. Characterization of Aceclofenac

For pre-formulation studies, the micronized form of Aceclofenac was subjected to physical tests.

4. Drug – Excipients Compatibility Studies

For the selection of suitable additives or excipients while developing a pharmaceutical formulation it’s necessary

to check the drug- excipients compatibility. Various organoleptic (macroscopic) properties were observed using this study. Drug excipients compatibility tests give the assurance of the stability of formulation. The active drug was mixed with Potassium bromide (KBr) and spectra were plotted on FT-IR. Accordingly, the excipient and Potassium bromide mixed in the same ratio as 9:1 ratio and spectra were plotted. The FT-IR band of Aceclofenac was checked with FT-IR spectra of Aceclofenac with other additives used. Shifting or Disappearance of Aceclofenac peak in spectra was examined.

4.1 Procedure

Aceclofenac was mixed with various excipient used in the study in the ratio as given in table 0.0, then filled in glass vials along with low-density polyethylene stopper with holes in the stopper and subjected to a different condition like room temperature,60˚C and 2-8˚C for four weeks. After the completion of the specified period, blends were tested for their physical change and moisture content.

Table 1: API- Excipient compatibility test.

S. No.	Ingredients	Drug: Excipients Ratio
1	Span 20	1:1
2	Tween 20	1:1
3	Liquid Paraffin	1:1
4	Propylene Glycol	1:1
5	Methyl Paraben	1:1
6	Carbopol	1:1
7	Menthol	1:1
8	HPMC K4 M	1:1
9	Purified Water	1:1

All the excipients were evaluated with the drug for compactability studies. The preformulation studies were performed according to the formula and results were recorded based on the data was obtained accordingly.

5. Characterization of Active Drug

The active drug was evaluated for various parameters through the standard test and accordingly the results have been mentioned in following table-

Table 2: Result analysis of Aceclofenac.

Test	Specification	Observation	Conclusion
Description	White color powder	White color powder	Complied
Odor	Odorless	Odorless	Complied
Solubility	Highly soluble in water	Practically Highly soluble in water	Complied
	Partially soluble in methanol	Practically partially soluble in methanol	Complied

6. Drug-excipient compatibility studies

The drug was evaluated along with all the excipients for compatibility studies and the results were recorded as per the data obtained after completion of the studies in following table-

Table 3: Drug-excipient compatibility data.

S. No.	Drug+ Excipient	Condition		
		Room Temperature	Hot air oven	Freezing Temperature
1	ACECLOFENAC (API)	Unchanged	Unchanged	Unchanged
2	API + SPAN 20	Unchanged	Unchanged	Unchanged
3	API + TWEEN 20	Unchanged	Unchanged	Unchanged
4	API + CARBOPOL 934	Unchanged	Unchanged	Unchanged
5	API + HPMC K4 M	Unchanged	Unchanged	Unchanged
6	API + LIQ. PARAFFIN	Unchanged	Unchanged	Unchanged
7	API + PROPYLENE GLYCOL	Unchanged	Unchanged	Unchanged
8	API + MENTHOL	Unchanged	Unchanged	Unchanged
9	API + METHYL PARABEN	Unchanged	Unchanged	Unchanged

7. Determination of λmax of Aceclofenac using a UV spectrometer

Max. Absorbance (λmax.) of Aceclofenac was determined by UV visible spectrophotometer by scanning drug samples between 203-280 nm and spectra were found.

8. Identification of Drug

FT-IR spectroscopy technique was used for the identification and evaluation of drug and excipients. Drug KBR pellets were used to record the FT-IR spectrum with a Perkin-Elmer model.

8.1 FT-IR spectroscopy technique

FT-IR spectroscopy method was used for the evaluation of the drug, there were several stretching's observed between C-H, C-N, and C-O. For the scanning process, the pure form of the drug was used. The IR spectra were taken by mixing Potassium bromide with the drug. In FT-IR spectra the functional groups showing Characteristics peaks.

8.2 Preparation of Aceclofenac stock solution (100µg/ml) in 0.1N NaOH

The drug (Aceclofenac) 100 mg was completely dissolved in 0.1N NaOH in a volumetric flask of 100 mL capacity.

9. Formulation Development

The material and method required for the formulation of the Emulgel and the associated evaluation parameter of the latter are explained in the following section.

9.1 Method for the preparation of the Aceclofenac Emulgel

A sum of 3 preparations were developed using various steps. The different formulation prepared for Aceclofenac Emulgel is given in the below table-

The steps used in the preparation of Emulgel were as follows:

Molecular dispersion technique with micronized active drug Aceclofenac by using excipients, the process will be the same for every trial batch from Batch No. F1 – Batch No. F3 for the manufacturing of Emulgel.

Process -1: - Material Sifting

Aceclofenac, Span 20, Tween 80, Carbopol 934, Liq. Paraffin, Propylene Glycol, HPMC K4M, Methyl Paraben shall be sifted through #20, #40 and filter through a suitable filter separately.

Process– 2: - Manufacturing Process

Here, two formulations were prepared by same method but they differed only in their type of gelling polymer used to formulate gel. The preparation method of emulsion was same. Gel was prepared by dissolving 1gm of Carbopol 934 and HPMC K4M separately in purified water (50 ml) with constant stirring at optimum speed by mechanical stirrer. The pH was adjusted by TEA (triethanolamine) to 6-6.5. The emulsion was prepared by following method, the Oil phase was prepared by dissolving span 20 in liquid paraffin. Then the drug was added to the above mixture. The aqueous phase was prepared by dissolving Tween 20 in purified water. Methyl paraben was dissolved in propylene glycol separately and this mixture was added to above mixture with constant stirring. Both oil and aqueous phases are heated to 70-80°C. Then oil phase is added to aqueous phase with constant stirring until to get cooled to temperature to form emulsion with constant stirring (Pravallika & Priyanka 2019).

Table 4: List of Ingredients and their quantities required during different Experimental Formulations of Emulgel of Aceclofenac.

Sr. No.	Ingredients	Approx. Quantity Required (g)
1	Span 20	0.262
2	Tween 20	0.021
3	Liquid Paraffin	0.021
4	PG	0.045
5	Methyl Paraben	0.045
6	Carbopol	1.151
7	Menthol	0.027
8	HPMC K4 M	0.006
9	Purified Water	0.006
	Total Weight	1.626

3.4.3 Process – 3: - Analysis

Emulgel Formulations are analyzed as per the official guidelines for all parameters and a comparative study shall be done with the existing market brand.

Table 5: F1-F3 Formulation for Emulgel.

Sr. No.	Ingredients	Unit Formula (g)		
		F-1	F-2	F-3
1	Aceclofenac	1.5	1.5	1.5
2	Span 20	1	1	1
3	Tween 20	0.5	0.5	0.5
4	Liquid Paraffin	7.5	7.5	7.5
5	PG	5	5	5
6	Methyl Paraben	0.03	0.03	0.03
7	Menthol	3	3	3
8	Carbopol	1	0	0.5
9	HPMC K4 M	0	1	0.5
10	Purified Water	1.5	1.5	1.5
Net Wt. / Tab. in mg		21.03	21.03	21.03

10. Evaluation Protocol of Emulgel (Pani et al. 2014; Yadav et al. 2016).

10.1 Physical tests
The prepared Emulgel was found optimum in terms of their color, grittiness, appearance & viscosity.

10.2 Rheological Study
The consistency was dictated by utilizing Brooke field viscometer DV II+ Pro, a cone and plate kind of viscometer with axle no 52. The instrument was collected and room temperature was kept up with at 25°C all through try. The emulgel whose consistency was to be estimated was weighed about 0.5 gm and set in plate and shut. Then the spindle is allowed to run and the viscosity was measured at 0.2 rpm.

10.3 Measurement of pH
The pH was recorded using the digital pH meter under ambient & standard conditions.

10.4 Skin Irritation Test
For this study, 4 rats were used. Animals were removed for their skin hairs and then applied the emulgel to check the irritation if happens.

10.5 In-vitro Drug Release Study
The in-vitro drug release i.e., in-vitro diffusion study was performed by Franz diffusion (FD) cell using phosphate buffer (pH 7.2) as medium. Cellophane membrane-used as semi-permeable membrane. 20 ml of medium was filled in receptor compartment up to the mark of collection limb. Then membrane was placed on the receptor compartment.

Cellophane membrane is used as semi-permeable membrane for diffusion. Receptor compartment up is filled with 20 ml medium up to the mark of collection limb. Then membrane is kept on the receptor compartment.

Accurately weigh 1 gm of emulgel and place on the membrane in between donor and receptor compartment and fit them firmly. The rotation per minute (rpm) of magnetic stirrer in the donor compartment and external stirrer are adjusted in such a way to make laminar flow in the medium. 5 ml of sample is collected on different time intervals from the collection limb and replace the same volume with buffer medium. Then the samples are analyzed by UV-spectrophotometer at 276 nm wavelength and thus concentrations are determined.

10.6Swelling Index
In this methodology, 1 gm of emulgel is taken on aluminum foil (permeable) and afterward positioned in a container containing 10 ml 0.1N Sodium hydroxide (NaOH). Then, at that point tests were taken out from the containers (at various time breaks) and put it on dry spot. Samples were weighed again as they were dried.

Swelling index is calculated by using following formula-

$$\text{Swelling index (SW) \%} = [(Wt - Wo)/Wo] \times 100$$

RESULTS AND DISCUSSION

1. Evaluation of Emulgel Formulation
1.1Rheological Properties of Emulgel
The different formulations of Emulgels were evaluated for their rheological properties. Formulation no. 1, 2 and 3 were analyzed at RPM 0.2. At shear stress of 165.8 for F1 demonstrated the viscosity of 13950. For F2 at shear stress 170.6 the viscosity was noted as 15526. At last, for F3 at shear stress of 170.6 the viscosity was found as 14526. By exhibiting such viscosity strengths, all the formulation were found as suitable emulgel having the optimum level of rheological properties.

Table 6: Rheological Properties of Emulgel.

Formulation	Spindle No.	RPM	Shear Stress	% T	Viscosity (c Ps)
F1	32	0.2	165.5	90	13950
F2	32	0.2	170.6	80	14526
F3	32	0.2	170.6	80	14526

1.2 In-vitro drug release test
The in-vitro drug release study was recorded from 0.5 hr to 8 hrs. Formulation no. 1, 2 and 3 demonstrated a time dependent drug release. The optimum drug release was found at 8 hours.

Table 7: In-vitro drug release test.

Time (hr)	% drug release		
	F1	F2	F3
0.5	12.2 + 0.56	9.92 + 0.48	9.92 + 0.48
1.0	16.2 + 0.46	14.02 + 0.38	15.3 + 0.22
1.5	18.4 + 0.86	19.10 + 0.78	18.7 + 0.29
2.0	22.2 + 0.86	24.01 ± 0.98	24.12 ± 0.68
2.5	31.1 + 0.44	30.12 + 0.12	31.12 + 0.38
3.0	32.2 ± 0.76	32.42 ± 0.48	31.12 ± 0.18
3.5	34.5 + 0.26	34.44 ± 0.23	34.32 ± 0.88
4.0	36.8 + 0.56	37.02 + 0.48	36.12 + 0.38
5.0	38. + 0.16	40.32 + 0.28	40.52 + 0.38
6.0	41.6 + 0.76	43.05 ± 0.28	43.12 ± 0.78

7.0	45.2 + 0.56	47.12 ± 0.28	47.32 ± 0.68
8.0	68.2 + 0.26	61.52 ± 0.38	71.22 ± 0.33

1.3 Physical Examination

Emulgel formulations were observed for physical examinations as follows-

Color : Yellowish white
Consistency : Viscous
Appearance : Glossy
Grittiness : No

1.4 pH estimation

The pH was estimated for different preparations as below mentioned-

Table 8: Estimation of pH.

S. N.	Formulation	pH
1.	F1	6.1
2.	F2	6.4
3.	F3	6.3

1.5 Skin Irritation Test

The rats were explored with formulation no. 1, 2 and 3 for 24 hours. During their time of exposure, all the rats were examined for harmful effects such as inflammation, redness and irritation at any part of the rat's skin.

1.6 Drug Content Estimation

The amount of drug was found to be 1.32mg, 1.31mg and 1.31mg in 1 gm of Emulgel formulation no. 1, 2 and 3.

Table 9: Drug Content Estimation.

S. N.	Formulation (1gm)	Drug Content (mg)
1.	F1	1.32
2.	F2	1.31
3.	F3	1.31

CONCLUSION

Emulgel of all set of batches were evaluated after the preparation for several pre-prescribed pharmacopeial and in-house standards and parameters Physical Examination, Rheological Study and Measurement of pH.

Future of pharmaceutical sciences of drug design and development will focus on the topical delivery systems because of huge drawbacks in oral, parenteral/ other routes showing high patient compliance. Ability of loading of hydrophobic drug in the hydrophilic gel matrix was found a solution by the development of Emulgel. Emulgel contains the excellent bio-adhesion, optimum viscosity with long-term stability. In this study, Emulgel were prepared by using two different gel forming polymers. Two formulations (out of three) were excellent in their elegance and absorption. In-vitro drug release test demonstrated that Carbopol-934 was the best polymer to formulate Emulgel with 64.04% w/w of drug release than HPMC-K4M as 57.30% w/w. Aceclofenac (emulgel) can be used as anti-nociceptive & anti-inflammatory for topical delivery. Aceclofenac Emulgel was successfully formulated and evaluated for authentic and selective parameters. Emulgel better enhances the topical delivery of even poorly soluble drugs like aceclofenac.

This research comes under the New Drug Delivery System (NDDS) that enhances the new approach in frequent dermal delivery of loaded Aceclofenac topical emulgel. It would be very impactful with easier, adequate sustained dosing at desired site with minimal systemic side effects in individual's sensations of pain and inflammation.

In the coming years, skin drug conveyance will be utilized broadly to grant better tolerant consistence. Since emulgel is useful in improving spreadability, attachment, thickness and expulsion, this novel medication conveyance become well known. Additionally, they will end up being an answer for stacking hydrophobic medications in water solvent gel bases for the drawn-out steadiness (Khullar et al. 2012).

Doubtless, the emulgels of aceclofenac will the top procuring dosage form having the better therapeutic potential and less patient complications.

REFERENCES

1. Archana G L, M. Sadanandam, Nalini Shasthry, Ch. Anil Kumar Preparation and Evaluation of Aceclofenac Topical Emulgels. Journal of Scientific Research in Pharmacy, 2014; 3(1): 12 – 15.
2. Gokani Preet N, Mittal Maheshwary, Pragnesh Patani. Formulation development and evaluation of Aceclofenac loaded Emulgel. International Journal of Sciences & Applied Research, 2019; 6(4): 06-15.
3. Grau M, J Guasch, J L Montero, A Felipe, E Carrasco, S Julia. Pharmacology of the potent new non-steroidal anti-inflammatory agent aceclofenac. Arzneimittelforschung, 1991; 41(12): 1265-76.
4. Kumar Davinder, Jasbir Singh, M. Antil, V. Kumar. Emulgel- Novel Topical Drug Delivery System- A Comprehensive Review. *IJPSR*, 2016; 7(12): 4733-4742.
5. Pani P C Sathya Keerthi, C Haranath, C Suryaprakash Reddy, A Chaitanaya Kumar, M Kiran Kumar, D Rushi Kumar Reddy, V Umapathi, B Yamuna, R Raviprakash Reddy. Emulgel: A Novel Approach for Enhancing Topical Delivery of Aceclofenac, 2014; 2015(1): 1-5.
6. Patel Japan, Brijesh Patel, Hardeepsingh Banwait, Kaushal Parmar, Manish Patel, 2011.
7. Formulation And Evaluation of Topical Aceclofenac Gel Using Different Gelling Agent. International Journal of Drug Development and Research, 3(1): 156-164.

8. Patil A K, Avinash B. Gangurde And Purnima D. Amin. Comparative Study Of Different Formulations Of Aceclofenac As A Topical Drug Delivery System And It's In Vitro And In Vivo Characterization. Ijpsr, 2014; 5(8): 3401-08.
9. Pravallika Ala, Ala Priyanka Reddy. Formulation and Evaluation of Aceclofenac Topical Emulgel. International Journal of Advanced Technology and Innovative Research, 2019; 10(2): 43-48.
10. Sharma Vivek, S K Nayak, S. R. Paul, B. Choudhary, S. S. Ray, Kunal Pal. 9- Emulgels. *Polymeric Gels*, 2018; 251-264.
11. Verma Amit, Ankit Jain, Ankita Tiwari, Sanjay K Jain. Emulgels: Application, 2017.
12. Potential in Drug Delivery. Functional Biopolymers, 343-371.
13. Yadav Sunil Kumar, Manoj Kumar Mishra, Anupamaa Tiwari, Ashutosh Shukla. Emulgel: A New Approach For Enhanced Topical Drug Delivery. IJCPR, 2017; 9(1): 15-19.
14. Gualda Battle E, I. Roma J, J. Carbonell A, J. T. Molina, J. F. Busquets, "Aceclofenac vs paracetamol in the managementof symptomatic osteoarthritis of the knee: a double-blind6-week randomized controlled trial," Osteoarthritis and Cartilage, 2007; 15: 900-908.
15. Jagannathan Hema, A. Thota, Ashok K. B. K, Githa K, A comparative study of aceclofenac versus etoricoxib in the management of acute low back pain in a tertiary care hospital," Journal of Drug Assessment, 2020; 9(1): 60-65.
16. Bushra Rabia, M. H. Shoaib, N. Aslam, I. N. Muhammad, "Aceclofenac: A New Effective and Safe NSAID," IJDDT, 2013; 4(1): 34-42.
17. Bhattarai S, H. P. Chhetri, Kadir Alam, P. Thapa, "A Study on Factors Affecting Low Back Pain and Safety and Efficacy of NSAIDs in Acute Low Back Pain in a Tertiary Care Hospital of Western Nepal," Journal of Clinical and Diagnostic Research, 2013; 7(12): 1-6.
18. Alsaleem M A, "Dysmenorrhea, associated symptoms, and management among students at King Khalid University, Saudi Arabia: An exploratory study," J Family Med Prim Care, 2018; 7(4): 769–774.
19. Urquhart E, "Analgesic agents and strategies in the dental pain model," Journal of Dentistry," 1996; 22(6): 336-341.
20. Chen et al., "Osteoarthritis: toward a comprehensive understanding of pathological mechanism," Bone Research, 2017; 5: 16044.
21. Guo et al., "Rheumatoid arthritis: pathological mechanisms and modern pharmacologic therapies," Bone Research, 2018; 6: 15.
22. Zhu et al., "Ankylosing spondylitis: etiology, pathogenesis, and treatments," Bone Research, 2019; 7: 22.
23. Sandoval M. A, Daniel H. Vaquero, "Preventing peridural fibrosis with nonsteroidal anti-inflammatory drugs," Eur Spine Journal, 2008; 17(3): 451-455.
24. Chunduri et al., Efficacy of aceclofenac and diclofenac sodium for relief of postoperative pain after third molar surgery: A randomised open label comparative study," Journal of Pharmacology & Pharmacotherapeutics, 2013; 4(2): 144–145.
25. Raza et al., "Topical Delivery of Aceclofenac: Challenges and Promises of Novel Drug Delivery Systems," Biomed Research International, 2014; 406731.
26. Koly et al., "Analysis of aceclofenac and bovine serum albumin interaction using fluorescence quenching method for predictive, preventive, and personalized medicine," EPMA Journal, 2015; 6: 24.
27. Shreevidya V. S, "An Overview on Emulgel," International Journal of Pharmaceutical and Phytopharmacological Research, 2009; 9(1): 92-97.
28. Samala M L, Sridevi G., "Role of Polymers as Gelling Agents in the Formulation of Emulgel," Polym Sci., 2016; 1(2).
29. Godbole et al., "Formulation, Development and Evaluation of a Novel Polymer-based Anti-Inflammatory Emulgel of Aceclofenac," Science International, 2018; 6: 71-79.
30. Khullar et al., "Formulation and evaluation of mefenamic acid emulgel for topical delivery," Saudi Pharmaceutical Journal, 2012; 20(1): 63-67.
31. Hardenia et al., "Emulgel: An Emergent Tool in Topical Drug Delivery," IJPSR, 2014; 5(5): 1653-60.
32. Sah et al., "Development and Evaluation of Tioconazole Loaded Emulgel," IJAP, 2017; 9(5): 83-90.
33. Yam et al., "General Pathways of Pain Sensation and the Major Neurotransmitters Involved in Pain Regulation," International Journal of Molecular Sciences, 2018; 19(8): 2164.
34. National Academies Press (US), "Pain and Disability: Clinical, Behavioral, and Public Policy Perspectives," 1987.