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FORMULATION AND EVALUATION OF TOPICAL GELS INCORPORATED WITH SOLID DISPERSIONS OF AN ANTIINFLAMMATORY DRUG

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Abstract

Formulation and development of a most effective product from poorly soluble drugs is one of the most challenging tasks in pharmaceutical industries. Solid dispersion is an efficient solubility enhancement method to overcome the solubility problem. The aim of this study was to formulate topical gels incorporated with solid dispersion of Aceclofenac to enhance permeability through the skin. Aceclofenac solid dispersions were prepared using suitable hydrophilic carriers to increase its aqueous solubility. In this study, solid dispersions of Aceclofenac were prepared by solvent evaporation and co-grinding method with two different hydrophilic carriers such as polyvinyl pyrrolidone (PVPk-30), and HPMC E15 LV. These were used in the ratio of (drug: carrier) 1: 1, 1:2 & 1:3 respectively. Evaluation parameters for formulation optimization were drug content, percentage practical yield, DSC, in-vitro dissolution studies & FTIR. The optimized SD (F3) solid dispersion is incorporated in topical gels of different concentrations prepared by using two gelling agents such as Carbopol 934 and HPMC K100M. From the results of in-vitro dissolution studies it was found that formulation F3 containing PVP k30 (1 : 3 ratio of drug: PVP k30) shows a higher dissolution rate compared with other formulations and pure drug. Optimized solid dispersion was incorporated into topical gels prepared by using two gelling agents in different concentrations. From the stability data obtained, no significant changes in physical appearance, viscosity, pH, and drug contents were seen. The present research work could be concluded as a successful production of topical gels incorporated with Aceclofenac solid dispersion. Improvement in aqueous solubility and thereby greater skin permeation is expected.

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Introduction

Aceclofenac is used as a non-steroidal anti-inflammatory drug indicated for the symptomatic treatment of pain and inflammation, osteoarthritis, rheumatoid arthritis and ankylosing spondylitis [1]. Oral administration of aceclofenac is associated with gastrointestinal side effects like gastric ulceration, gastrointestinal bleeding and liver and kidney trouble .Aceclofenac is increasingly administered by topical route. The topical route of administration eliminates side effects, increases patient compliance, avoids first-pass metabolism, and maintains the plasma drug level for a longer period [2]. Aceclofenac has a poor aqueous solubility that may cause a problem with skin permeation [2]. Aim of this study was to formulate topical gel incorporated with solid dispersion of aceclofenac to enhance permeability through skin.

Methodology

Pre formulation Study

Drug-Excipient interaction study using FTIR Spectroscopy

The spectra of physical mixture were compared with that of standard drug.

Preparation of Solid dispersion

Aceclofenac solid dispersions were prepared by using hydrophilic carriers like polyvinyl pyrrolidone K30 and Hydroxypropyl methylcellulose E15LV in proportions 1:1 (drug: carrier) (100mg:100mg), 1:2 (drug: carrier) (100mg: 200mg) and 1:3 (dug: carrier) (100mg:300mg) were prepared by using following methods.

Physical mixtures

The physical mixtures were prepared manually by mixing pre-weighed amounts of aceclofenac and carriers (PVP K-30 and HPMC K15LV).

Solvent evaporation method

Solid dispersions of aceclofenac with PVPk-30 were prepared by dissolving the drug and carriers in the ratios of 1: 1, 1:2 and 1:3 in solvent ethanol to get a clear solution. The solvent was then evaporated at 40 to 45°C with continued mixing to get dry mass. The obtained dry masses were kept in a desiccator until solid dispersions attains constant weight. The solidified masses were passed through sieve No. 44 to get fine powder.

Co-grinding method

Accurately weighed pure drug powder and the carrier were physically mixed for some time. The powder mixture was then ground. Then the sample was collected and kept at room temperature in a screw capped glass vial until use.

Table 1:Different batches of Aceclofenac solid dispersion

	Solvent evaporation			Co-grinding		
	F1	F2	F3	F4	F5	F6
Aceclofenac	1g	1g	1g	1g	1g	1g
PVP K30	1:1	1:2	1:3			
HPMC K15 LV	-	-	-	1:1	1:2	1:3
Ethanol	_	_	_	10 ml	10 ml	10 ml

Evaluation of solid dispersion

The solid dispersion prepared were further studied for percentage practical yield, drug content, *in vitro* release studies, FTIR and DSC study.

Drug content determination

Solid dispersions equivalent to 10 mg of aceclofenac were weighed accurately and dissolved in the 10 ml of methanol. The solution was filtered, diluted suitably and drug content was analyzed at 273 nm by UV spectrophotometer

Percentage Practical Yield:

Solid dispersions were collected and weighed to determine practical yield (PY) from the following equation.

$$PY\ (\%) = \frac{\text{Practical Mass (Solid dispersion)}}{\text{Theoretical Mass (Drug+ Carrier)}} \times 100$$

Invitro dissolution study

Invitro release profiles for each solid dispersion as well as pure drug were performed using USP type II dissolution apparatus. Sample was filled in capsules[F1&F4(100mg), F2&F5(200 mg), F3&F6(300mg)]& kept in the basket of dissolution apparatus containing 900ml phosphate buffer pH 7.4 at 37± 0.5ºC and stirred at 50 rpm. Aliquot of 5ml was withdrawn at time intervals of 0,2, 5, 10, 15, 30, 45 & 60 min. The withdrawn volume was replaced with the same volume of dissolution medium in order to keep the total volume constant. The absorbance of the sample was measured 273 nm after suitable dilution using appropriate blank.

Differential Scanning Calorimetry Study (DSC study)

DSC was used to analyze the curves of Aceclofenac, carriers & SDs representing the rates of heat uptake. DSC study was done at IIT Madras.

Preparation Of Gel

Two different gelling agents such a carbopol 934 and HPMC K100 M were used to prepare gels.

Procedure For Preparation Of Gel

Carbopol 934: The formulations were prepared by soaking carbopol 934 and HPMC K100M in different concentrations (0.5,1,1.5,2 %) in 60 ml of water for 24 hrs. Then added glycerol and dimethyl sulfoxide with continuous stirring. The solid dispersion containing 1.5% drug was dissolved in ethanol and this solution was added to the above gel with continuous stirring. The prepared formulations were filled in suitable bottles and stored in cool place.

Table 2:Formuation of gel using Carbopol934

Ingredients	F3C1	F3C2	F3C3	F3C4
Solid dispersion equivalent to 1.5% drug	1.8 g	1.8 g	1.8 g	1.8 g
Carbopol 934	0.5	1	1.5	2
Glycerol	5 ml	5 ml	5 ml	5 ml
Dimethyl sulfoxide	0.25 ml	0.25 ml	0.25 ml	0.25 ml
Distilled water	Up to 100 ml	Up to 100 ml	Up to 100 ml	Up to 100 ml

HPMC K100M:

Weighed quantities of Hpmc socked in 60ml of water for 24hrs and then add glycerin and dimethyl sulfoxide. The solid dispersion containing 1.5% drug was dissolved in ethanol and this dry solution was added to above gel with continouns stirring.

Table: 3 Formulation of gel using HPMC K100 M

Ingredients	F3H1	F3H2	F3H3	F3H4
Solid dispersion equivalent to 1.5% drug	1.8 g	1.8 g	1.8 g	1.8 g
HPMC K100 M	0.5	1	1.5	2
Glycerol	5 ml	5 ml	5 ml	5 ml
Dimethyl sulfoxide	0.25 ml	0.25 ml	0.25 ml	0.25 ml
Distilled water	Up to 100 ml	Up to 100 ml	Up to 100 ml	Up to 100 ml

Evaluation of gel

Physical evaluation

The prepared gels were visually inspected for clarity, color and homogeneity.

Determination of pH

pH of formulation determined by dispersing 0.5 gm of gel in 50 ml of water.

Determination of Viscosity

The viscosity of gel formulations were determined using Brookfield's viscometer.

Determination of Spreadability

Two glass slides of standard dimensions were selected. The gel formulation was placed over one of the slide. The other slide was placed on the top of the gel in such a way that the gel was sandwiched between the two slides. A 20 g weight was kept on the upper slide. The time taken for upper slide to travel and separate away from the lower slide under the influence of weight was noted.

Spreadability= M.L/T

M-wt. given on upper slide

L- length of glass slide

T-time taken in sec

Determination of Extrudability

The formulation under study was filled in a clean, aluminum collapsible tube. It was then placed in hardness tester. The

plunger was adjusted to hold the tube properly. The pressure was applied for 30 seconds. The percentage of gel extruded was calculated.

Determination of drug content

100 mg of gel was dissolved in methanol & filtered and the volume was made to 100 ml with methanol. The resultant solution was suitably diluted with methanol. The absorbance of the resulting solution was measured at 273 nm.

In-vitro diffusion study

In vitro skin permeation studies were carried out using Franz diffusion cell. Cellophane membrane was mounted between the donor and receptor compartment of the diffusion cell. The formulated gel was placed over the membrane. The receptor compartment of the diffusion cell was filled with a phosphate buffer. The solution in the receptor compartment was stirred continuously using a magnetic bead at 50 rpm, with the temperature maintained at 32 ± 0.5 °C. The samples were withdrawn at different time intervals and analyzed for drug content using a UV–Vis spectrophotometer at 273 nm. The receptor compartment was replenished with an equal volume of the same medium. The cumulative percentage diffused was plotted against time.

Ex vivo skin permeation studies

Ex vivo release study was conducted using fresh chicken skin from slaughter house. The skin was soaked in phosphate buffer pH 7.4 solution for 5-6 hours and washed with water. The dermis was dried at 25% RH, wrapped in aluminium foil and stored in freezer until further use.

For *ex vivo* permeation studies, skins were allowed to hydrate for 1 hour before being mounted on the Franz diffusion cell with the stratum corneum facing the donor compartment. The sample was applied on the skin and then fixed in between donor and receptor compartment of Franz diffusion cell. Required quantity of phosphate buffer (pH 7.4) was placed in the receptor compartment and the temperature of the medium was thermostatically controlled at 37±10^{0}C by the surrounding water jacket and the medium was stirred. Aliquots of 1 ml were withdrawn at predetermined intervals and were spectrophotometrically estimated at 273 nm.

Cloth staining study

This study was undertaken to assess the fabric staining property of the gels. Fabrics of different fiber blends ranging from 100% cotton to 100% polyester were procured and stained with 0.5 gm gels of Aceclofenac and observed for staining after washing.

Stability study

For stability study, the gel sample were stored at 40^{o}C, 60% RH, in stability chamber. The physical appearance, pH value, Viscosity and drug content were periodically analysed for 1 month.

Comparative study of optimized gel with prepared Aceclofenac gel

Selected formulation was compared with prepared gel of Aceclofenac**.** The aceclofenac gel was prepared using a gel base and diffusion study of gel is done for 12 hrs and is compared with the optimized solid dispersion incorporated gel of aceclofenc.

Results and Discussion

Preformulation Studies

Drug-Excipient Interaction Study Using FTIR Spectroscopy

The FTIR spectra of Aceclofenac, physical mixture I (aceclofenac+ PVP k30), physical mixture II (Aceclofenac + HPMC k15 LV) is recorded to check any interaction between drug and polymer. The characteristic peak obtained after FTIR indicates that there is no chemical interaction between drug, PVP K30, and HPMC K15 LV.

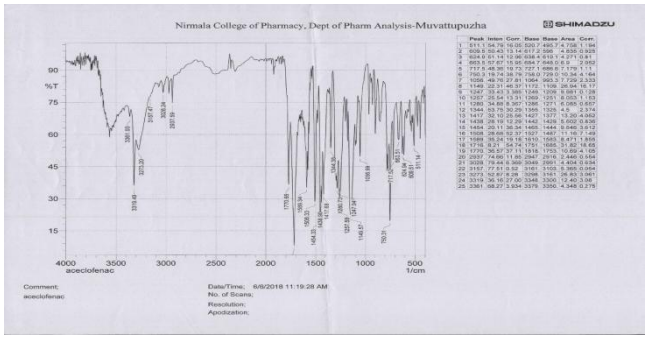

Fig 1: FTIR Spectra of Aceclofenac

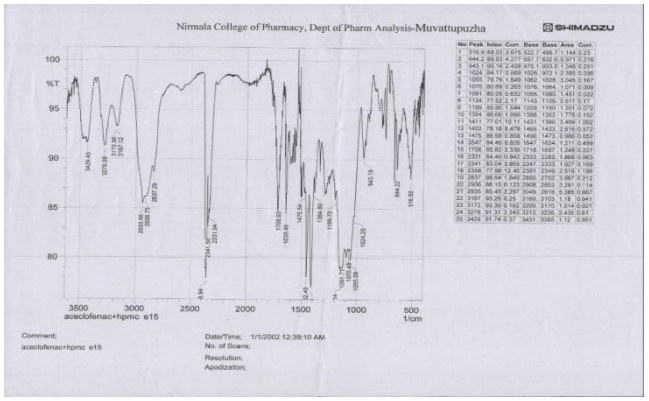

Fig 2: FTIR spectra of Aceclofenac and HPMC E15 LV

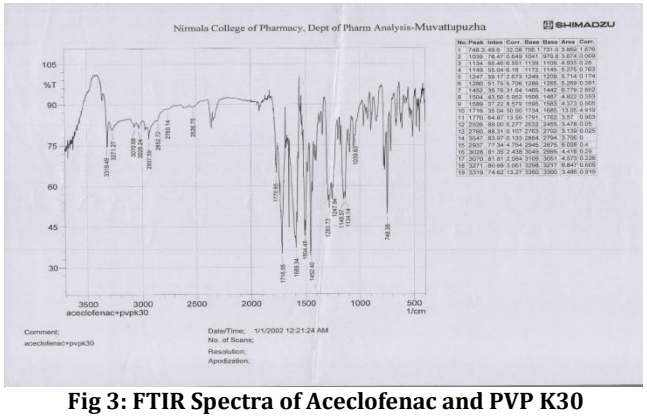

Fig 3: FTIR Spectra of Aceclofenac and PVP K30

Preparation of solid dispersions

Solid dispersions using different ratios of Aceclofenac and carriers such as PVP K30 and HPMC EI5 LV is prepared by solvent evaporation and co-grinding method.

Evaluation of Solid dispersions

Drug content

The percentage drug content of the formulations were analyzed using UV spectroscopy. All formulation shows a percentage drug content between 77.68% to 97.09%.

Percentage practical yield

The results of Percentage practical yield for all formulations of solid dispersions were found to be 89.09 to 95.46%

In-vitro drug release study

The *in- vitro* release studies of different batches of solid dispersions are shown in Fig: 4. The solid dispersion prepared by solvent evaporation method in the ratio 1:3 shows improved dissolution when compared with pure drug and co-grinding method. The formulation F3 shows greater solubility than the others.

The study reveals that there is increase in the dissolution rate of all the Aceclofenac solid dispersions when compared to pure aceclofenac itself (Fig no.4). This may be due to the increase in drug wettability, conversion to amorphous form and solubilization of the drug due to hydrophilic carrier. From the *In-vitro* drug release profile, it can be seen that formulation F3 containing PVP K30 (1:3 ratio of drug: PVP K30) shows higher dissolution rate compared with other formulations. The increase in dissolution rate is in the order of F3 >F6>F2 >F4>F1>F5.

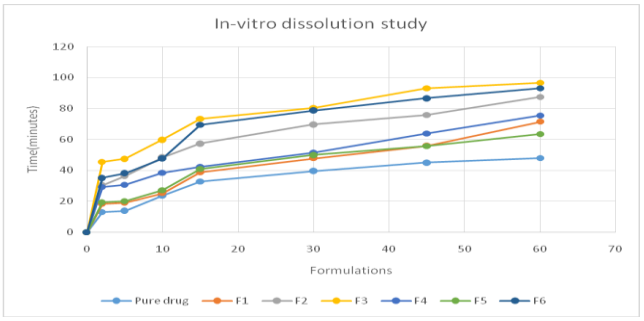

Fig 4: Release profiles of solid dispersion

DSC Study

In the DSC study, pure Aceclofenac showed a sharp endothermic peak at 153.8^{0}c corresponding to the melting point of drug and the sharpness of peak indicates crystalline nature of the drug. The carrier PVP K30 showed endothermic peak at 82.2^{0}c. The DSC curve of physical mixture of the drug and carrier (PVP K30) showed two broad endothermic peaks, one peak at 64.3^{0}c corresponding to carrier and the other peak at 126.0 ^{0}c corresponding to drug. The peak temperature in the physical mixture were slightly shifted with respect to the drug and carrier alone. In case of Aceclofenac solid dispersion (1:3 ratio of drug & carrier), the endothermic peak were broadened and shifted towards a lower temperature (66.3^{0}c) with reduced intensity. The DSC thermogram revealed the diminishing of the characteristic peak of the drug. This may due to the uniform distribution of drug in the polymer, resulting its better solubilization in the carrier and conversion of crystalline to amorphous form.

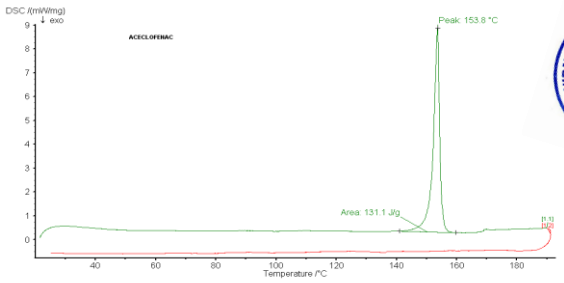

Fig 5: DSC thermogram of aceclofenac

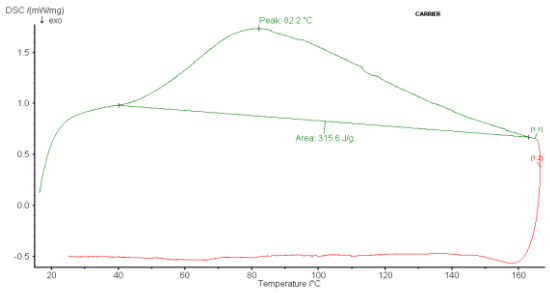

Fig 6: DSC thermogram of carrier (PVP K30)

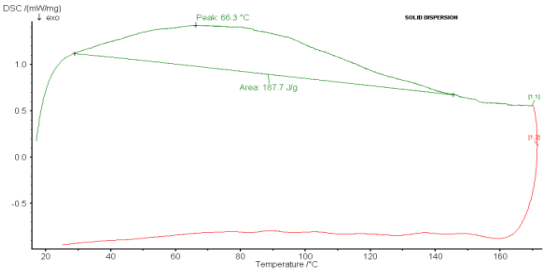

Fig 7: DSC thermogram of physical mixture

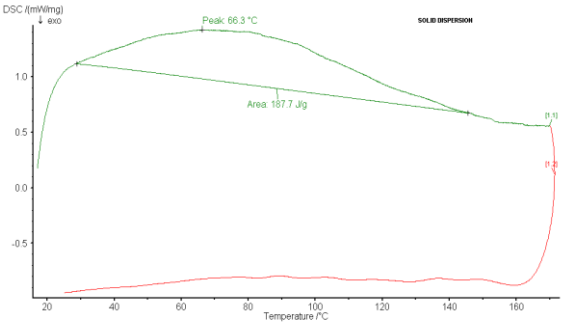

Fig 8: DSC thermogram of Solid dispersion (F3)

Preparation Of Gels

Topical gels incorporated with optimized aceclofenac solid dispersion(F3) were prepared using different concentrations of gelling agents such as Carbopol 934 & HPMC K100 M Eight formulations were prepared and the prepared gel formulations were optimized on the basis of evaluation studies.

Evaluation of Topical Gels Incorporated With Aceclofenac Solid Dispersion

Physical evaluation

The prepared gel formulations were examined visually. All batches of gel formulations showed good homogeneity with absence of lumps.

Determination of p H

The pH of all the prepared gel formulations were found to be in the range of 6.2 – 7.3 which lies in the normal pH range of skin.

Determination of viscosity

The measurements of viscosity of the prepared gels were done with a Brookfield Viscometer. Viscosities were found to be proportional to the concentration of the gelling agent.

Cloth staining

This study is very important to ascertain the patient compliance of the gels. Patients generally resist gels as they stain clothes. It was observed that all the eight gels did not stain any of the fibre blends tested, even after prolonged exposure and accelerated drying.

Determination of spreadability

The value of spreadability indicates the degree of shear required to apply the gel. Lesser the time taken for separation of two slides, better the spreadability. Values of spreadability indicate that the gel formulations are easily spreadable.

Determination of extrudability

Extrudability of all the formulations is higher than 80%. All the formulations showed good acceptance properties. The extrusion of the gel from the tube is an important parameter during its application and in patient acceptance.

Drug content

The drug content of formulations was in the range of 88.90-96.66 %.

In-vitro diffusion study

In-vitro drug release study was performed by Franz diffusion cell method using phosphate buffer p H 7.4.

From the data obtained it was found that the prepared topical gel of carbopol 934 of concentration 1(F3C2) releases 68.54 % drug by *in-vitro* diffusion study over a period of 8 hrs.

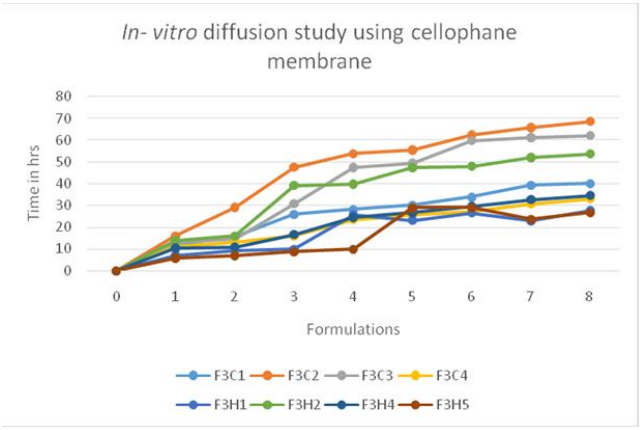

Fig 9:*In vitro* diffusion study using cellophane membrane

Formulation batch F3C2 showed good release profile compared to other formulations prepared by using Carbopol 934 & HPMC K100 M. Increase in concentration of gelling agent leads to decreased drug release from formulations which may be due to increase in viscosity of formulation.

Ex-vivo drug permeation study

Ex-vivo study was also done for the gel formulations prepared by using two gelling agent such as carbopol 934 & HPMC K100 M. Fig 10 show graphical presentation of release profile. The cumulative amount of drug permeated at the end of 8 hrs was found to be (63.63%)for formulation F3C2(gelling agent Carbopol 934 of concentration 1%) which was found to be higher than that of other formulations.

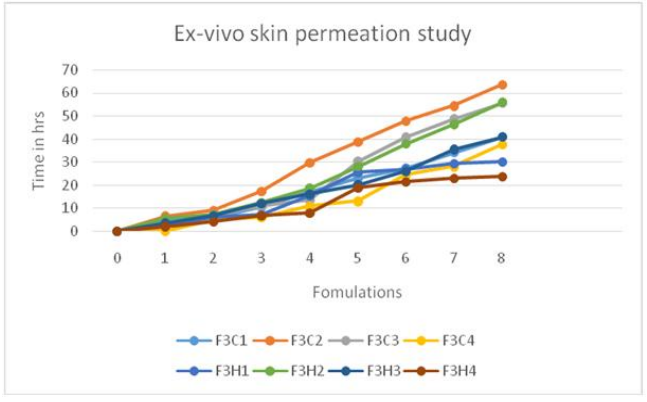

Fig 10*: Ex-vivo* drug permeation study

Stability study

The selected formulation (F3C2) were subjected to stability testing. Changes in the appearance, pH, viscosity, and drug content of the gel were investigated at a period of 1 month. From the data obtained, no significant changes in physical appearance, viscosity, pH & drug content were seen. This indicates the stability of prepared gel formulation

Comparative study of optimized topical gel with prepared Aceclofenac gel

It was found that the cumulative percentage of drug diffused from optimized formulation(F3C2) of topical gel incorporated with aceclofenac solid dispersion is higher than that of plain aceclofenac gel(Fig 11).Hence, it proves that the solid dispersion improves solubility and thereby permeation of the drug.

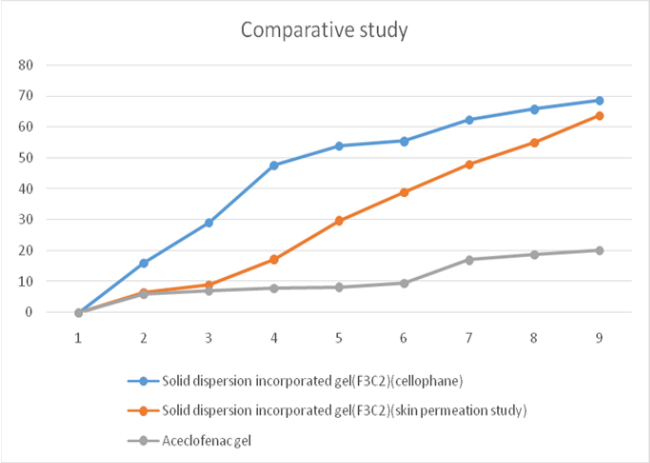

Fig 11: Comparative *in vitro* diffusion study of optimized topical gel with prepared Aceclofenac gel

Conclusion

Carbopol 940 topical gel containing Aceclofenac solid dispersion was successfully prepared. These formulated gels showed sustained permeation of Aceclofenac over 8h in *ex vivo* skin permeation study. The gels were characterized by pH, viscosity, spreadability, extrudability and cloth staining tests. FTIR study clearly indicated the absence of any significant interaction between the drug, Aceclofenac and other excipients present in the formulation.

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Not Declared

Conflict of interest

Authors are declared that no conflict of interest.

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Ethical consideration and inform consent

Not applicable

References

1. R.Natarajan, G. Komala, TR. Ramcy, Swathi Polineni and S. Mohan, Dissolution enhancement of Aceclofenac solid dispersion prepared with hydrophilic carriers by solvent evaporation method, IJRPC 2014;,4(1):798-899.
2. T.V Rao , S Vidhyadhara Enhancement of dissolution rate of aceclofenac by solid dispersion technique,2009;7(1):93-98.
3. Kumar Tarun Guleri, Kaur Loveleen Preet.Formulation and evaluation of topical gel: a recent approach for novel drug delivery.Asian journal of biomedical pharmaceutical science. 2013;3(17):1-5
4. Nava Dayan, Pathways of skin permeation, Cosmetics 7 Toileteries magazine,120,2005
5. Shilpi Sinha, Sanjula Baboota, Solid dispersion an alternative technique for bioavailability enhancement of poorly soluble drugs,Journal of dispersion science and technology,30(10),2009.
6. Serajuddin AT, solid dispersion of poorly water soluble drugs,Journal of pharmaceutical science,1999
7. Khalid Bashir Mir, Nisar Ahmed Khan, Solid dispersion –an overview of the technology,International journal of pharmaceutical sciences and research,2017
8. Mark T Davis, Amorphous solid dispersions of BCS class ii drugs: A rational approach to solvent and polymer selection, Chemical engineering research and design,110,2016
9. Chivate Niranjan, Sidharth Patil, A complete review on solid dispersion technology and factorial design, Researchgate,2012.
10. Michal Benes,Methods for the preparation of amorphous solid dispersions-A comparative study,Journal of drug delivery science and technology,38,2017.
11. Satish Kumar Gupta, S. Kumar, Preparation and Evaluation of solid dispersions of aceclofenac for the improvement of dissolution rate. Journal of chronotherapy and drug delivery 2015;2(6):74-86
12. Sachin Kumar Singh, K. Gowthamarajan, Dev Prakash, Somashekhar C.N Dissolution enhancement of poorly soluble aceclofenac by solid dispersion technique and its comparison with marketed formulations. International journal of pharma tech 2010;2(4):1256-1576
13. Ankit Gupta, Mahesh Kumar Kataria, Neetu Khatri, An overview on techniques implemented for dissolution enhancement of glipizide, International journal of pharmaceutical and chemical science,3(1),2014.
14. M. A Chauhan, Kalyani prakasam, Divakar goli, Formulation and evaluation of gel containing fluconazole antifungal agent, international journal of drug development and research, 3(4), 2011.
15. Sonia Dhiman, Parmjit Kaur, Sandeep Arora, Solid dispersions: Opportunity in drug delivery system, Drug invention today, 797(45), 2012.