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Formulation and Evaluation of Transdermal Gel of Nimesulide and Effect of Permeation Enhancers on its Release Characteristics

Mr Lateef [1], Gandhi Kinjal B[2]*, Mr. Anwar[4] Dr. P Ajith Kumar[3]

[1,4] Malik Deenar College,Seethangoli,Kerala, India, [2] Assistant Professor, Department of Pharmaceutics,Malik Deenar College of Pharmacy,Seethangoli, Kerala, India

Correspondence: Gandhi Kinjal B, Assistant Professor, Malik Deenar College of Pharmacy, Seethangoli ,Bela Post, Kasargod Kerala.

Email; gandhikinjal471@gmail.com,

RESEARCH ARTICLE

ABSTRACT:

The present study was undertaken to formulate and evaluate transdermal gel of Nimesulide. Nimesulide is a non-steroidal anti inflammatory drug used to relieve the pain and inflammation. Transdermal gel has gained more and more importance because the gel based formulations are better percutaneously absorbed than creams and ointment bases. Therefore, transdermal gel of Nimesulide was prepared using different polymers such as Sodium alginate, Sodium CMC, Methyl cellulose, and HPMC and prepared gel using different concentrations of sodium CMC as polymer, selected optimised polymer concentration P3 and incorporated permeation enhancer PEG 400 at different proportions. The study encompasses compatibility studies using FTIR spectra, drug content, viscosity, spreadability, and pH determination. Further the optimized formulation F2 was evaluated by *in vitro* diffusion study. Optimized formulation batch F2 subjected to stability study. The preliminary compatibility studies conducted revealed that there was no interaction between Nimesulide and excipients. *In vitro* drug release study was carried out with Franz diffusion cell using natural egg membrane in pH 7.4 phosphate buffer as diffusion medium. Formulation batch F2 containing Sodium CMC and permeation enhancer PEG 400 showed 99.20 % drug release at 180 min and 7.98 g.cm /sec spreadability. Result showed that formulation batch F2 showed better drug release at 3 hrs. Formulation batch F2 was used further for stability study. Stability studies conducted under accelerated condition were shown satisfactory results. It was concluded that Sodium CMC gel containing Nimesulide showed good consistency, spreadability, homogeneity and stability. So, Transdermal gel had wider prospect for transdermal preparations.

Key words: Nimesulide, Sodium CMC, PEG400, Transdermal gel of Nimesulide.

INTRODUCTION

More recent approach to drug delivery is to deliver the drug in to systemic circulation at a predetermined rate which is known as controlled release drug delivery system. Such systems helped to overcome the side effects associated with conventional systems of medication, which require multidose therapy.Transdermal therapeutic systems are defined as self contained, discrete dosage forms which when applied to intact skin deliver the drug(s), through the skin at a controlled rate to systemic circulation. Thus it is anticipated that, transdermal drug delivery system can be designed to input drugs at appropriate rates to maintain suitable plasma levels for the therapeutic efficacy by using skin as a port of entry of drugs[1].

Nimesulide is a non steroidal anti inflammatory drug, which acts by selectively inhibiting the cyclooxygenase-2 (COX-2)[2].It showed better anti-inflammatory and analgesic activity.[2,3,8]Nimesulide is well tolerated in short term treatments, but in case of long term treatments requires higher doses of 200 mg/day, the incidence of side effects are greater[3].Therefore to minimise the adverse effects, to extend the drugaction, to improve the delivery of the drug through skin we attemped to formulate the suitable TDDS of Nimesulide.

Classification of penetration enhancers [7]

1. Terpenes: E.g. Nerodilol, Menthol, 1,8 Cineole, Limonene, Carvone etc.
2. Pyrrolidones: E.g. N-Methyl-2-Pyrrolidone, Azone
3. Fatty acids and esters: E.g. Oleic acid, Linoleic acid, Lauric acid, Capric acid etc.
4. Sulfoxides and similar compounds: E.g. Dimethyl sulfoxide,N,N-Dimethyl Formamide
5. Miscellaneous enhancers: E.g. Phospholipids, Cyclodextrins, Amino acid derivatives,

Enzymes etc.

Advantages of transdermal gels:

1. Avoids the first pass hepatic metabolism
2. Drug delivery can be easily eliminated in case of toxicity.
3. Fewer side effects as there is reduced plasma concentrations of drugs.
4. Dosing frequency get reduced which increases the patient compliance.
5. Through transdermal gels drug is delivered in a steady rate over an extended period of time.
6. Conventional dosage forms follow a peak and valley pattern of drug release kinetics in blood and tissue. Transdermal drug delivery system is designed to release drugs at a predetermined rate and continuously avoiding unnecessarily high peaks and sub therapeutic troughs in plasma drug levels.
7. Increases the therapeutic value of many drugs as it avoids the problems associated with drugs e.g. GI irritation, nausea, vomiting, heartburn and increased appetite after oral therapy.
8. Provides ease of rapid identification of medication in emergencies, non-responsive patients, unconscious or comatose patients.
9. Equivalent therapeutic effect with lower dose of drug can be achieved than is necessary when drug is given orally.
10. Drugs that are degraded by enzymes and acids in the gastrointestinal system can be administrated by incorporating in transdermal gels.
11. Continuity of drug administration permitting the use of a drug with short biological half-life.

Transdermal Gel Forming Agents:(7,8)

For the preparation of gels, polymers are essential as they give the structural network. Such polymers are known as gelling agents. There are many gelling agents; some of the common ones are acacia, alginic acid, bentonite, Carbopols (now known as carbomers), carboxymethylcellulose, ethyl-cellulose, gelatin, hydroxyethylcellulose, hydroxypropyl cellulose, magnesium aluminum silicate (Veegum), methyl-cellulose, poloxamers (Pluronics), polyvinyl alcohol, sodium alginate, tragacanth, and xanthan gum. Gel forming polymers are classified as follows:

1. Natural polymer
   a) Proteins
      - Collagen
      - Gelatin

b) Polysaccharides
- Agar
- Alginic acid
- Sodium or Potassium carrageenan
- Tragacanth

2. Semisynthetic polymers
   a) Cellulose derivatives
      - Carboxymethyl cellulose
      - Methylcellulose
      - Hydroxypropyl cellulose
3. Synthetic polymers
   a) Carbomer
      - Carbopol -940
      - Carbopol -934
      - Carbopol -941
   b) Poloxamer
   c) Polyacrylamide
   d) Polyvinyl alcohol
4. Inorganic substances
   - Aluminium hydroxide
   - Bentonite
5. Surfactants
   - Cetostearyl alcohol
   - Brij – 9

MATERIALS AND METHODS

Materials:

Nimesulide was purchased from 'Yarrow chem products, Mumbai'.The other chemicals include Sodium alginate, Sodium CMC, HPMC, Methylcellulose, PEG-400, Glycerin were obtained from our college laboratory. All the chemicals were used as received without any further treatment and purification.

PREFORMULATION STUDIES [8]

Preformulation may be described as a phase of the research and development process where the formulation scientist characterizes the physical, chemical and mechanical properties of new drug substances, in order to develop stable, safe and effective dosage forms. Ideally the preformulation phase begins early in the discovery process such that the appropriate physical and chemical data is available to aid the selection of new chemical entities that enter the development process.During this evaluation, possible interaction with various inert ingredients intended for use in final dosage form was also considered in the present study. The following data must be considered.

Drug - Excipient Compatibility Study

Excipients are integral components of almost all pharmaceutical dosage forms. The successful formulation of a stable and effective solid dosage form depends on the careful selection of the excipients, which are added to facilitate administration, to promote the consistent release and bioavailability of the drug and protect it from degradation. API and excipients were been thoroughly mixed in predetermined ratio given in below table and passed through sieve number 40. The blend was filled in transparent glass vials and were closed with gray coloured rubber stoppers and further sealed with aluminum seal and charged in to stress condition at above condition. Similarly API should also be kept at all condition as for the samples. Samples were withdrawn for analysis within two day of sampling date as per the compatibility study plan. Physical observation should be done at every week up to 1 month and FTIR study was carried out to determine the compatibility of excipients with the drug.

Preparation of Transdermal gels

1% w/w nimesulide gel was prepared using different concentrations of polymers such as sodium alginate, HPMC, Sodium CMC, Methylcellulose.The formulation of various gels with different polymers are shown in [Table 1] .

Procedure:

Accurately weighed amount of Polymers in four different ratios were placed in known amount of distilled water. After complete dispersion the polymer solution was kept in dark for 24 hours for swelling.Accurately weighed amount of Nimesulide was dissolved in a suitable solvent. The drug solution was added slowly to polymeric dispersion, Finally the remaining

ingredients were added to form a homogeneous molecular dispersion.

Evaluation of Gels:

Viscosity Measurement [17,18]

Brookfield digital viscometer was used to measure the viscosity of prepared gel formulations. The spindle no. 6 was rotated at 10 rpm. The reading, near to 100% torque was noted. Samples were measured at 30 ±1°C.

Spreadability[19]

One of the criteria for a gel to meet the ideal quantities is that it should possess good spread ability. It is the term expressed to denote the extent of area to which gel readily spreads on application. The therapeutic efficacy of a formulation also depends upon its spreading value It was determined by wooden block and glass slide apparatus. Weights of about 2g were added to the pan and the time was noted for upper slide (movable) to separate completely from the fixed slides.

Spread ability was then calculated by using the formula:

$$S = \frac{M.L}{T}$$

Where,

S = Spreadability

M = Weight tide to the upper slide

L = Length of a glass slide

T = Time taken to separate slide completely from each other.

Homogeneity[21]

All developed gels were tested for homogeneity by visual inspection after the gels have been set in the container. They were tested for their appearance and presence of any aggregates.

Drug Content [22]

A specific quantity (1g) of developed gel was taken and dissolved in 100ml of phosphate buffer of pH 7.4. The volumetric flask containing gel solution was shaken for 2 hours on mechanical stirrer in order to get complete solubility of drug. The solution was filtered through 0.45 µm membrane filter and estimated spectrophotometrically at 293 nm using phosphate buffer (pH 7.4) as blank.

***In-vitro* Drug Diffusion Study [23]**

In-vitro drug release studies were performed by using a modified Franz diffusion cell with a receptor compartment capacity of 100ml. Egg membrane was mounted between the donor and receptor compartment of the diffusion cell.The formulated gels were weighed up to 1 g and placed over the drug release membrane and the receptor compartment of the diffusion cell was filled with phosphate buffer (pH 7.4). The whole assembly was fixed on a magnetic stirrer, and the solution in the receptor compartment was constantly and continuously stirred using magnetic beads at 50 RPM. The temperature was maintained at 37 ± 0.5°C. The samples of 5ml were withdrawn at time interval of 15, 30, 60, 90, 120, 150, 180, and 210 minutes. Analysed for drug content spectrophotometrically at 293nm against blank. The receptor phase was replenished with an equal volume of phosphate buffer at each time of sample withdrawal. The cumulative amounts of drug diffused from gels were plotted against time.

Drug Release Kinetics:

MECHANISM OF DRUG RELEASE

Various models were tested for explaining the kinetics of drug release.

To analyse the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi model, Hixon Crowell model and Korsmeyer-Peppas release model.

Zero Order Release Rate Kinetics To study the zero–order release kinetics the release rate data are fitted to the following equation.

$$F = K_o t$$

Where,

F is the drug release,

K_o is the release rate constant

t is the release time.

The plot of percentage drug release versus time is linear.

First Order Release Rate Kinetics: The release rate date are fitted to the following equation **Log (100 – F) = Kt**

A plot of log % drug release versus time is linear.

Higuchi Release Model To study the Higuchi release kinetics, the release rate data were fitted to the following equation,

$$F = K t^{1/2}$$

Where,

K is the Higuchi constant.

In higuchi model, a plot of percentage drug release versus square root of time is linear.

Hixon-Crowell Model: To study the Hixon-Crowell release kinetics, the release rate data were fitted to the following equation,

$$W_o^{1/3} - W_t^{1/3} = k t$$

Where,

Wo is the original mass/weight of drug,

Wt is the mass/weight at 't' time,

K is Hixon-Crowell constant.

In this model ($Wo^{1/3} - Wt^{1/3}$) versus time is linear.

Korsmeyer And Peppas Release Model

The release rate data were fitted to the following equation,

$$M_t / M_\infty = k.t$$

Where,

M_t / M_∞ is the fraction of drug released

K is the release constant

n is diffusion exponent

If n is equal to 0.89, the release is zero order. If n is equal to 0.45 the release is best explained by Fickian diffusion, and if $0.45 < n < 0.89$ then the release is through anomalous diffusion or non-fickian diffusion.

Results and Discussion:

Compatibility Studies:

From this it can be concluded that the drug has maintained its identity without losing its characteristic properties. It will not show any adverse effect in action of the formulation and helps to study desired parameters in the present study.

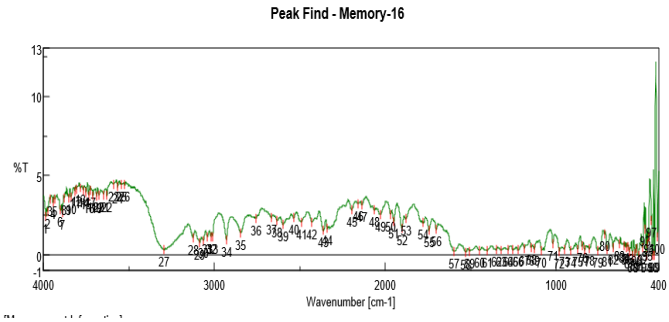


Figure 1: FTIR SPECTRA of Nimesulide

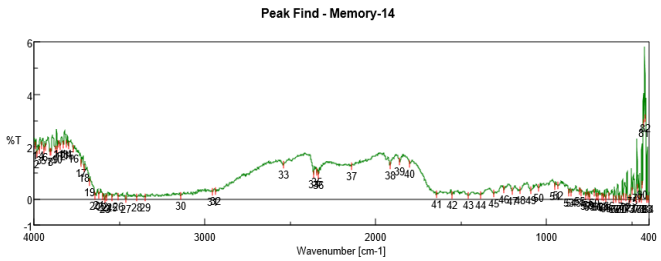


Figure 2: FTIR Spectra of Nimesulide and excipient physical mixture

Viscosity

The viscosity of the transdermal gel formulations generally reflects its consistency. The results of viscosity measurement of Nimesulide transdermal gel containing different concentration (0.2, 0.4, 0.6 and 0.8g) of Sodium CMC showed in the table. The viscosity of P1, P2, P3, and P4 gel formulations can be ranked according to their viscosity values as follows: (351789 ± 1.10) > (324713 ± 0.73) > (278072 ± 0.85) > (233168 ± 0.92) > (205361 ± 0.58) cps. A result showed that as the concentration of polymer increases, viscosity of gel formulations also increases. But at the high concentration of polymer may affect the *in vitro* drug release and spreadability of gel formulations.as shown in table 2.

Table 2: Viscosity measurements of preliminary trial batches P1 to P4

Batch No.	Viscosity (cps)
P1	205361 ± 1.10
P2	233168 ± 0.73
P3	278072 ± 0.85
P4	324713 ± 0.92

Values are mean value of 3 observation (N=3) and values in parenthesis are standard deviation (± SD)

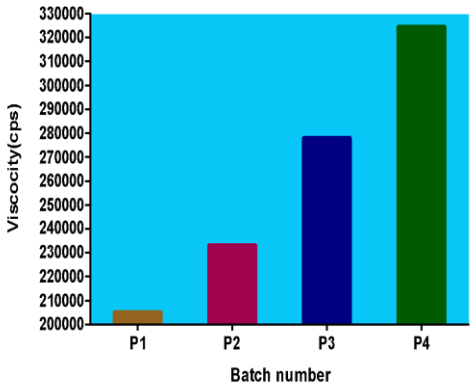


Figure 3: Viscosity measurement of P1 to P4

In Vitro Release Study

The total amount of drug released for a fixed period of 4 hour was found to decrease with increase in sodium CMC concentration. The *in-vitro* drug release of P1, P2, P3 and P4 gel formulations can be ranked according to their drug release values as follows: (97.49%) > (95.52%) > (93.83%) > (89.73%).(Figure: 4) The result showed that as the concentration of sodium CMC polymer increases, *in-vitro* drug release of gel formulations decreases. Even though a good drug release was observed with 0.2g sodium CMC concentration, as it was too soft and less viscous in nature, and an optimum polymer concentration of 0.6g which showed good consistency was selected for further study on drug release. The result showed that, as the concentration of permeation enhancer increases, the *in-vitro* drug release of gel formulations increases. Study revealed that PEG 400 release was maximum (99.20 %) over a period of 3 h at 2 mL permeation enhancer concentration level.

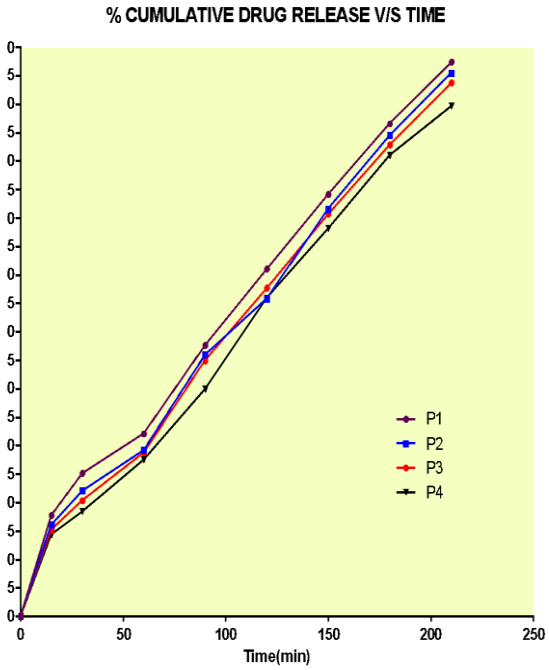


Figure 4: Invitro Release study of batches P1 to P4.

Spreadibility

The result showed that as the concentration of permeation enhancer increases, the spreadability of transdermal gel formulations also increases. Spreadability of batch was F3 <

F2 < F1. But there was not observed significant changes in spreadability between F1 to F3 formulation batches. All batches shows better spreadability.

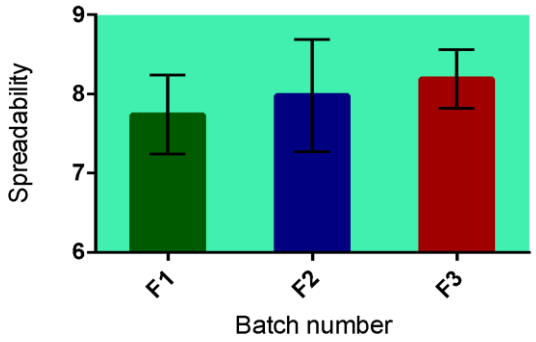


Figure:5 Spreadibility Measurement of F1 to F3.

Drug Content

Drug content defines the uniform distribution of drug in the formulation. Percentage drug content was measured for all transdermal gel formulations. Results of transdermal gel formulations revealed that the drug content was almost uniform in all the transdermal gels with low SD values. We can conclude that uniform drug loading of Nimesulide was found in gel formulation. (Figure 7)

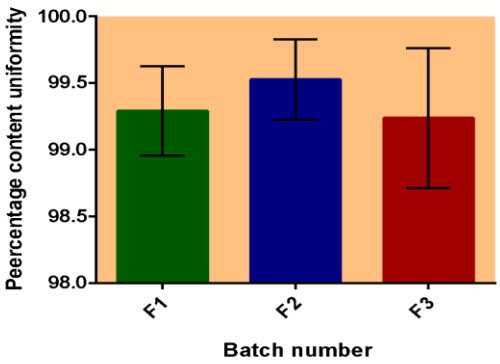


Figure 6: Drug content of formulations F1 to F3

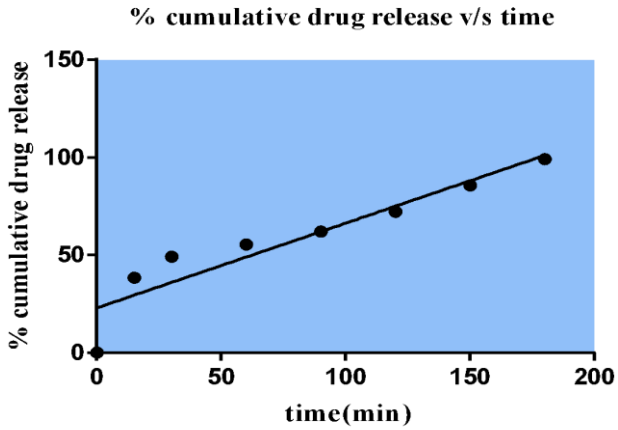
Drug Release study:

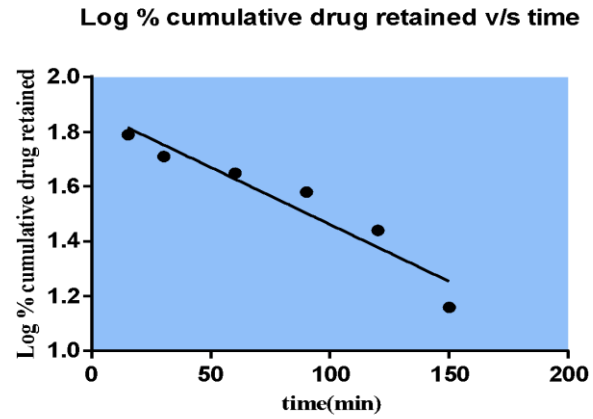
The in-vitro drug release data was subjected to goodness of fit test by linear regression analysis according to zero order, first order kinetic equations. Higuchi's and Korsmeyer model in order to determine the mechanism of the drug release.

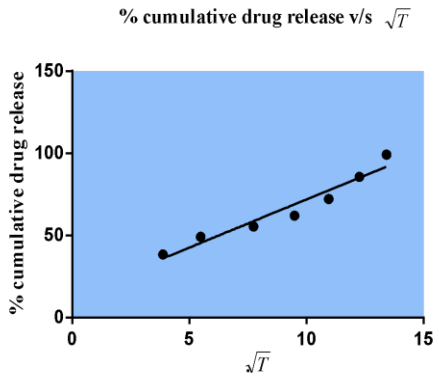
When the regression coefficient 'r' value of zero order and first order plots were compared, it was observed that the 'r' value of zero order plot was 0.87. where as the 'r' value of first order plot was 0.94 indicating drug release was not found to follow first order kinetics.

Figure showed the percent drug release versus square root of time plot. It was observed that the 'r' value for the Higuchi's plot was found to be 0.98 for the formulation studied indicated the release of drug from this formulation was governed by diffusion controlled process.

The Peppas model is widely used to confirm whether the release mechanism is Fickian diffusion, nonFickian diffusion or zero order. 'n' value could be used to characterize different release mechanisms. When Korsmeyer et al equation was fitted to dissolution data values, the exponent 'n' was found to be 0.35 indicating the drug release by Fickian diffusion.







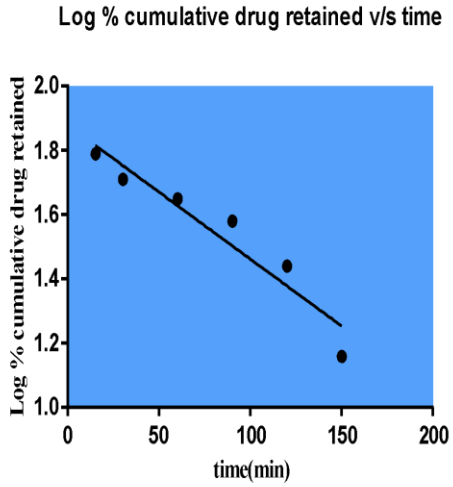


FIGURE 7: ZERO ORDER AND FIRST ORDER KINETICS ALONG WITH HIGUCHI AND PEPPAS MODEL

STABILITY STUDY

In any rational design and evaluation of dosage forms for drugs, stability of the active component must be a major criterion in determining their acceptance or rejection. Stability of the drug can be defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic and toxicological specification.

The international conference on Harmonization (ICH) guidelines titled 'stability testing of new drug substance and products' (Q1A) describes the stability test requirements for drug registration applications in the European union, Japan and USA.

Stability studies as per ICH guidelines,

Long-Term Testing : 25°C ± 2°C / 60% RH ± 5% for 12 months.

Accelerated Testing : 40°C ± 2°C / 75% RH ± 5% for 6 months.

Stability studies were carried out at 40°C ± 2°C / 75 ± 5% RH for the selected formulation for one month.

Method

The selected formulation was packaged in air tight plastic container or aluminium container. They were then stored at 40°C / 75% RH, for one month and evaluated for their physical appearance and drug diffused at specific interval of time per ICH guidelines.

Table 3: Stability study of Batch F2

Time(min)	In-vitro drug release of formulation batch F2	
	Initial	After 1 month stability study
0	0.00±0.00	0.00±0.00
15	38.40±0.64	36.93±0.12
30	49.23±0.15	48.53±0.38

60	55.41±0.24	53.84±0.62
90	62.10±1.33	61.79±0.78
120	72.23±1.03	71.64±1.22
150	85.70±0.73	85.25±0.85
180	99.20±0.95	99.04±0.53

Table Comparison of in-vitro drug release study of formulation batch F2 Sodium CMC transdermal gel after 1 month stability study

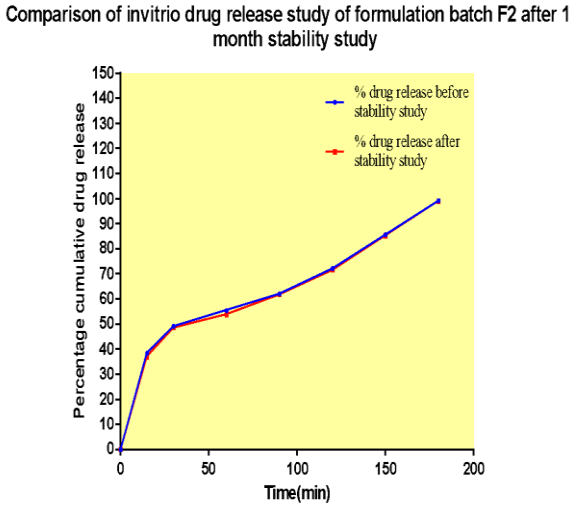


Figure 8 Comparison of in-vitro drug release study of formulation batch F2 Sodium CMC transdermal gel after 1 month stability study

Conclusion

This study confirms that transdermal gel of nimesulide with polymers is prepared along with permeation enhancer which enhances the release characteristics of drug.

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