

Research Article

Non-Pressurized Topical Spray of Diclofenac Diethylamine

Neelam Pawar^{*} and Hema Chaudhary

P. D. Memorial College of Pharmacy, Sector-3A; Sarai Aurangabad, Bahadurgarh, India

***Correspondence Info:**

Neelam Pawar,
P. D. Memorial College of Pharmacy,
Sector-3A; Sarai Aurangabad,
Bahadurgarh, India
Email: neelampawar5555@gmail.com

Keywords:

DDEA,
Non-pressurized topical spray,
Metering chamber,
Drug release,
Kinetics,
Stability

Abstract

The objective of research work was an attempt to develop non-pressurized topical spray formulation to improve diclofenac diethylamine permeation through lipoidal membrane obstruction. A prototype formulation and thirty formulations were prepared (using different concentration of permeation enhancer, cooling, buffering, film forming agent, plasticizer and lecithin), their characterization & optimization was done (FTIR spectroscopy, drug release, skin-irritation, kinetics study performed by construct the plot of zero order/first order/Higuchi/Korsmeyer Peppas's). A screw neck HDPE bottle procured with metered spray (200mcl) pump and actuator was selected as a dispensing system. The result demonstrated drug release of optimized formulation (F30) was found to be $93.3\% \pm 3.1 \mu\text{gcm}^{-2}$ and its *in vitro* study revealed significant plus immediate topical drug permeation. According to $n >$ value of F30 showed super case (II) transport, erosion release mechanism, moreover no skin-irritation source.

1. Introduction

Non pressurized topical spray does not contain any propellant so more user friendly, environmentally acceptable, by pass GIT tract to prevent GI irritation, cut down cost of formulation gives topical action, maximum amount of drug reaches to the site of action, maximum absorption of drug, ease of application and increase patient compliance. The ultimate goal of non pressurized topical delivery system to site specific delivery of drug to ensure the absorption through skin deferent methodologies have been investigated including use of drug derivatives, vehicle, film formers, solubilizer, permeation enhancer, plasticiser and buffering agent[1]. A non-steroidal anti-inflammatory drug i.e. Diclofenac Diethylamine (DDEA) with N-ethyl ethanamine (1:1) has allied selective inhibition of COX-2 enzyme (precursor of prostaglandins) which contribute a significant role in the pathogenesis of pain, inflammation, fever and inhibits production of proteoglycan in cartilage. The solubility of DDEA (Class II BCS drug) is depends on the pH of the surrounding solution and it undergoes an intermolecular cyclization in the acidic condition, which can cause its inactivation [2]. DDEA possesses other characteristics such as poor bioavailability (40-60%), short biological half life (2-3), high permeability are the foremost contemplation in release studies of pharmaceutical active candidate[3].

The non pressurized spraying dosage form can be solution/suspension in which the therapeutic agent and a choice of excipients are dissolved in the selected solvent system which are then filled in the spraying bottles [4]. Solution delivers the drug to the surface of the skin; drug is distributed by placing the device gently against the skin and triggering, causing it to discharge a light spray containing a proprietary formulation of the drug on the skin, the drug is then absorbed [5].

The key idea in non pressurized spray dispensing system, spray pump operate on the mechanical energy provide by depression of actuator, while aerosol valves operate on the energy provided by propellant in the system. The potential of HDPE bottle for packing of non pressurized spray are tremendous with shipment at reduced weight, immune from denting and breakage, less expensive handling, no possibilities of corrosiveness, proper labelling, application aided by improved adhesive and stretchability of labels. The versatility of container includes metering valves for delivering specific quantities

of product at each discharge to avoid wastage of formulation [6]. The actuators are available in different style depending upon the use like dental, dermal, through and oral with foldable and unfold able arms. The spray pump operates on mechanical energy provided by depression of actuator. The metering chamber communicates with composition by means of dip tube. By using metered dose pump it is possible to deliver precise amount of film on to skin and this in association with knowledge of concentration of physiologically active ingredient within the composition can serve to ensure that level of active ingredient tightly controlled. When actuating the pump, a piston moves descending in the metering chamber, prevent backflow into dip tube, generate pressure which force air previous to priming or liquid outward through actuator. When the actuation pressure is takes away, a spring will force the piston to go back to its initial position. This makes a vacuum in the metering chamber which pulls the liquid form the container by lifting up the ball from the ball seal over the dip tube at the underside of metering chamber [7].

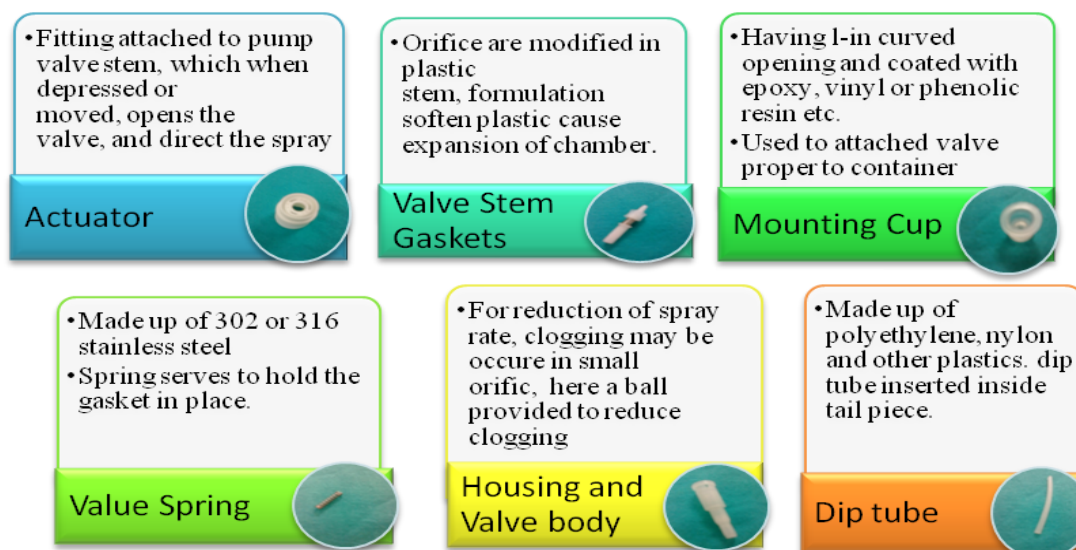


Fig. A: Spray valve component (actuator, valve, stem, gaskets, mounting cups, valve spring)

2. Materials and Method

The study sample consisted of chemicals and reagents: DDEA was obtained from Arti Drugs Ltd., India; ethanol (Hayman Ltd., England), isopropyl alcohol (Deepak Corporation Ltd., India), propylene glycol (Changshu Yangua Chemical Co. Ltd., China), menthol (Nector Life Science Ltd., India), Plasdone K-90 (ISP Pharmaceutical, USA), isopropyl myristate (Finar Chemical Ltd. India), Citric acid (Canton Lab Pvt. Ltd., India), Soya lecithin (Shree Nidhioils & food Pvt. Ltd., India) were used. Dialysis membrane (M. weight cut-off 12,000 Da) was obtained from Himedia Labs, India.

2.1 Selection of containers, spray pumps and actuators

Specially designed HDPE bottle, Screw type (Medsized, USA) were utilized for filling topical spray formulations. Pump (VP6/9018/415+) (Aptar Pharma Pvt. Ltd., India) were procured for nonpressurized spray delivery system based on physic-chemical compatibility of components with formulation. 200 mcl pump volume selected based on required dose of drug. Actuator (PR139.A01.RS3.L.TM) with actuating volume of 200 mcl was selected and used.

2.2 Non Pressurized Spray Formulation and Development

The spray developed as topical solution made up of non aqueous vehicle, plasticizer, permeation enhancer, buffering agent, emollient, film former, cooling agent. DDEA was dissolved in ethanol in a separate vessel until clear solution was obtained. The polymeric system was prepared by incorporating isopropyl alcohol and PVP into solvent system. With continuous stirring lecithin, propylene glycol, peppermint oil and isopropyl myristate was added to the mixture. (Table A). The pH was adjusted by adding citric acid into spray system. Volume of final solution was made up by ethanol in such a way that desired amount of drug could be obtained after each actuation, solution was stirred and pH was observed.

2.3 Characterization

The formulation was observed for organoleptic (color, physical state, odour & nature) and IR spectra of the

formulation recorded by scanning in wavelength region of 650-4000 cm^{-1} in a FTIR-Spectrophotometer (Jasco FT-761, FT-IR spectrophotometer). The amount of spray is transferred into a stopper volumetric flask (250ml) and was shaken with methanol (50ml) to extract the drug and filtered. The filtrate volume was made up to with methanol (50ml), pipette out (0.5ml) and its volume was made up to with methanol (25ml) [8].

2.3.1 Pump Delivery / Shot Weight

After dismissal one shot into air; one unit weighted and process repeated for ten times to determined the average weight delivery per shot[individual weight (divergence should be less than 6%, should not more than 10% from the average weight for passing pump delivery)] [9].

2.3.2 Evaporation Time and Weight Checking

The time needed for spray film to dry estimated by spraying the formulation on to ethanol sensitive paper and drying time was reported; the weight was done by periodically adding un-filled spray container to filling lines which after filling with concentrated are moved and reweighted [10].

Table A: Parameter Summarization of Spray Formulation (%W/W)

| Batch Codes | Quantitative Composition | | | | | | | | | |
|-------------|--------------------------|-------|---------|-------|----------------|---------|-------------|------|----------|-------|
| | Drug | IPA | Ethanol | IPM | Peppermint oil | Menthol | Citric acid | PK | Lecithin | PG |
| F1 | 4.64 | 45.86 | qs | - | - | - | - | - | - | - |
| F2 | 4.64 | 36.66 | qs | 10.00 | - | - | - | - | - | - |
| F3 | 4.64 | 31.36 | qs | 15.00 | - | - | - | - | - | - |
| F4 | 4.64 | 26.36 | qs | 20.00 | - | - | - | - | - | - |
| F5 | 4.64 | 31.16 | qs | 15.00 | 0.20 | - | - | - | - | - |
| F6 | 4.64 | 30.96 | qs | 15.00 | 0.40 | - | - | - | - | - |
| F7 | 4.64 | 29.96 | qs | 15.00 | 1.40 | - | - | - | - | - |
| F8 | 4.64 | 29.16 | qs | 15.00 | 0.20 | 2.00 | - | - | - | - |
| F9 | 4.64 | 27.16 | qs | 15.00 | 0.20 | 4.00 | - | - | - | - |
| F10 | 4.64 | 25.16 | qs | 15.00 | 0.20 | 6.00 | - | - | - | - |
| F11 | 4.64 | 30.36 | qs | 15.00 | 0.20 | - | 0.80 | - | - | - |
| F12 | 4.64 | 30.16 | qs | 15.00 | 0.20 | - | 1.00 | - | - | - |
| F13 | 4.64 | 29.96 | qs | 15.00 | 0.20 | - | 1.20 | - | - | - |
| F14 | 4.64 | 29.66 | qs | 15.00 | 0.20 | - | 1.50 | - | - | - |
| F15 | 4.64 | 29.36 | qs | 15.00 | 0.20 | - | 1.80 | - | - | - |
| F16 | 4.64 | 29.16 | qs | 15.00 | 0.20 | - | 2.00 | - | - | - |
| F17 | 4.64 | qs | - | 49.16 | 0.20 | - | 1.00 | - | - | - |
| F18 | 4.64 | - | qs | 45.16 | 0.20 | - | 1.00 | - | - | - |
| F19 | 4.64 | - | qs | 44.91 | 0.20 | - | 1.00 | 0.25 | - | - |
| F20 | 4.64 | - | qs | 44.76 | 0.20 | - | 1.00 | 0.40 | - | - |
| F21 | 4.64 | - | qs | 44.71 | 0.20 | - | 1.00 | 0.60 | - | - |
| F22 | 4.64 | - | qs | 40.91 | 0.20 | - | 1.00 | 0.25 | 4.00 | - |
| F23 | 4.64 | - | qs | 30.91 | 0.20 | - | 1.00 | 0.25 | 4.00 | 10.00 |
| F24 | 4.64 | - | qs | 44.51 | 0.20 | - | 1.00 | 0.25 | 0.20 | 5.00 |
| F25 | 4.64 | - | qs | 44.31 | 0.20 | - | 1.00 | 0.25 | 0.40 | 7.50 |
| F26 | 4.64 | - | qs | 44.11 | 0.20 | - | 1.00 | 0.25 | 0.60 | 10.00 |
| F27 | 4.64 | - | qs | 38.71 | 0.20 | - | 1.00 | 0.25 | 0.20 | 15.00 |
| F28 | 4.64 | - | qs | 36.21 | 0.20 | - | 1.00 | 0.25 | 0.20 | 20.00 |
| F29 | 4.64 | - | qs | 33.71 | 0.20 | - | 1.00 | 0.25 | 0.20 | 25.00 |
| F30 | 4.64 | - | qs | 29.71 | 0.20 | - | 1.00 | 0.25 | 0.20 | 15.00 |

IPA=Isopropyl Alcohol; IPM= Isopropyl Myristate; PG=Propylene Glycol; PK= Pladone K-90

For weight examination, a spray was fired into beaker, for extraction of diclofenac done with the help of methanol. This solution was further diluted with methanol (10ml). From this solution (1ml) was taken and diluted with methanol (10ml). Drug content was analyzed by UV-Visible spectrophotometer (Jasco-UV spectrophotometer) [11].

2.3.3 Delivered Dose Uniformity (Content Uniformity)

Metered-dose topical sprays containing solution within an apparatus able of quantitatively holding the dose leaving from actuator of the atomizing device. Shake the container (5sec) and discharge once to waste. Then, wait (5sec), shake (5sec), discharge again to waste and repeat this process for three actuations. After 2sec, fire one dose of the metered-dose topical spray into the collecting container by actuating the atomizing device & collect the contents of the collecting container by successive rinses. The content of drug in the collective rinses determine by evaluated the content uniformity at 6th, 7th, 8th, 82th, 83th, 84th, 164th, 165th, and 166th shots[12].

2.3.4 Skin Permeation Studies

The amount of permeation (application of fixed dose mimics) that would be in practical actual quantity of topical spray was actuated on the top of synthetic membrane with the help of 200mcl pump (0.5625g of formulation was applied on the surface area of 1.76 cm² of membrane) [13]. The receptor phase was phosphate buffer (pH 6.78) prepared by dissolved sodium hydroxide in water to produce a solution (40-60% w/v) & diluted with sodium hydroxide (8g in 1000ml) thermostated at 37 °C and stirred with a Teflon coated magnetic stirrer. Cellulose acetate membrane with thickness 0.13mm soaked in glycerin before use for 2 hr. The permeation depends on nature and type of diffusion cell used. A model receptor medium for an *in-vitro* permeability experiment should mimic the *in-vivo* condition [14].

2.3.4.1 Sampling

The best method of sampling depends on term of time interval, frequency and volume. Sampling was done (0.5 and 1hr), sample (0.5ml) was drawn and same was replaced in receptor media for *in-vitro* permeation experiments by using Franz diffusion cell [15]. The cellulose acetate synthetic membrane and skin was mounting on the receptor compartment as a permeation cell (10 ml of pH 6.8 phosphate buffer as receptor medium). The vehicle (1g) containing the test drug was taken as a donor compartment and covered with a paraffin paper. The receptor segment of cell is maintained (37°C) and mixed by a magnetic stirrer (600rpm). At predetermined time intervals, aliquots (1ml) of the receptor medium were withdrawn and immediately replaced by an equivalent volume of fresh receptor solution and analyzed by UV-method [16].

2.3.5 Release Kinetics

To find out the mechanism of drug release from the matrix, the release rate was fitted to equations (Zero-order equation: $Q=Q_0-k_0t$, where Q is the quantity of drug release at time t , and k_0 is the release rate; First-order equation: $Q=\ln Q_0-k_1t$, where k_1 is the release rate constant; Higuchi's equation: $Q=k_2t^{1/2}$, where Q = amount of drug release at time (t); k_2 = diffusion rate constant and Korsmeyer Peppas model: $M_t/M_\infty = Kt^n$, Where M_t / M_∞ is a fraction of drug released at time(t); k = release rate constant & n = release exponent).

2.3.6 Irritation Studies

The *Wistar* Rats (18 animals approved from the Institutional Animal Ethical Committee (IAEC), Protocol No. PDM/CPCSEA/RES/2013/1/1) were used & divided into groups (03); group 1 was served as normal, devoid of treatment; group 2 (Control was applied with standard irritant i.e. formalin solution) and topical optimized formulation spray onto nude skin of animals (Group 3) [17]. The Draize patch test was carried out using rat as animal model, sprayed area of shaved skin with tapes occluded and after 24 hr responses were recorded [18].

2.3.7 Stability Studies

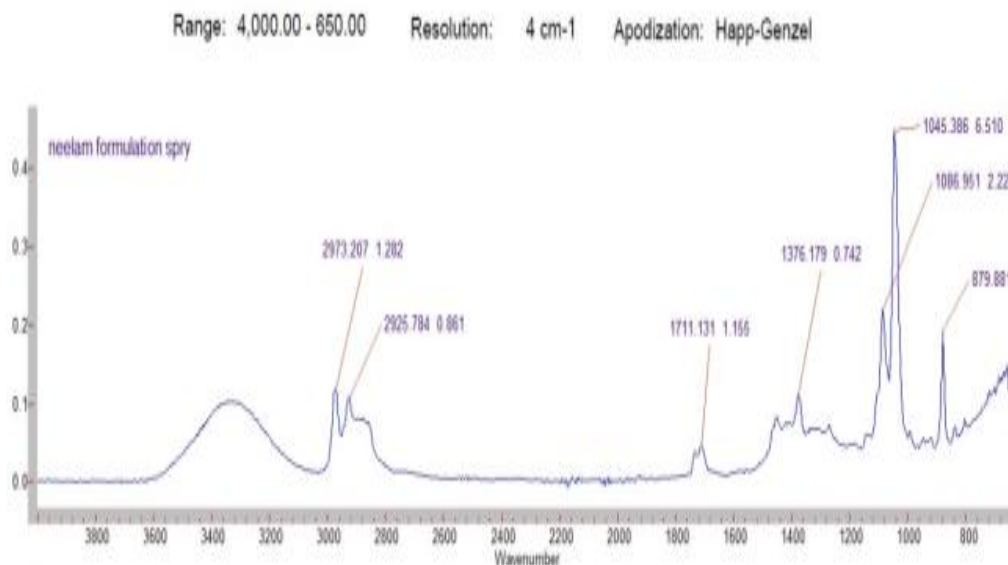
According to ICHQ1A (R2) guideline [19] stability results should assemble the proposed storage statement for labeling (if applicable), which should be based on the stability estimation of the API [20]. The API is considered as stable if it is within the defined/ regulatory terms, when stored at (30±2°C/65±5%RH) as long term stability for 0, 3, 6, 9, 12, 18 and 24 months; at (40±2 °C/75± 5% RH) as an accelerated stability for 0, 2, 3 and 6 months. The formulation was prepared, filled in final containers and initial testing was done for various parameters. 20 bottles were kept for 2, 3 and 6 months in accelerated stability chamber at 40±2 °C and 75± 5% RH and 50 bottles were kept for 3months, 6months, 9months, 1 year, 1^{1/2} years, 2years in real time stability chamber at 30±2 °C and 65±5% RH. The formulation was evaluated for change in physical appearance, pH, assay, evaporation time, average rate per actuation, uniformity of delivery dose and cumulative drug release.

3. Result and Discussion

The formulations were selected & optimized [F30 (Fig. B) and F18 for further studies] on based of clarity of solution, evaporation rate, spray pattern and tackiness of film formed.

The results of FTIR spectrums (Fig. B) exhibited characteristic peaks at 2973cm^{-1} (C-H aliphatic stretching); 1711cm^{-1} (C=O stretching); 879cm^{-1} (N-H bend) & 1376cm^{-1} for aryl C-N stretch and showed no possibility of chemical interaction between the drug and excipients in optimized formulation. The optimized formulation (F30) absorbance (0.695) was determined by UV-Spectrophotometer (methanol as a blank at λ_{max} 281nm.) and found drug content (calculated by $y = 0.051x - 0.093$) which complies with British Pharmacopoeia standard. This point concluded that the drug is distributed almost homogeneously and there was no loss of drug in formulation.

Fig. B: FT-IR spectra of Optimized Formulation (F30)



3.1 Pump Delivery and Shot Weight

The pump (200mcl) valve was actuated to fullest extend and container was re-weighted (g). So, specific gravity (equals to density of test solution to density of water) of solution was determined to identify the delivered dose per actuation (ml). Densities of both solutions were determined (not more than 10% individual weight deviates from average weight and deviation found to be less than 6%). The shot weight of all formulations; Max. & Min. value= 0.21ml & 0.20ml with value of Mean& Std. Dev. =0.20 & 0.004 respectively.

3.2 Evaporation Time & Weight Checking

The time required for spray film to dry was predicted by spraying the formulation on skin and drying time was noted down (F30 has 9 ± 0.59 minute, more drying time due to presence of PK-90 and propylene glycol in formulation than F18 (6 ± 0.24 minute)). The test complies if not more than two individual masses deviate by more than 25% from average valve and none of deviate by more than 35%. The weight standard deviation was 0.134g often containers (F30) with average weight 29.2g as compared to F18 (0.145g with average weight 29.1g).

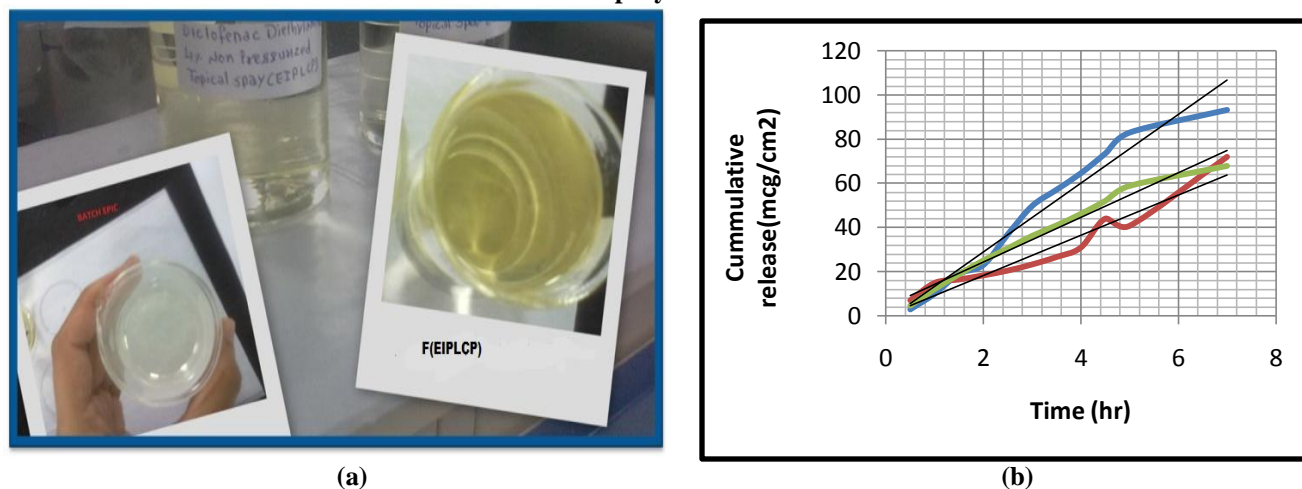
3.3 Delivered Dose Uniformity (Content Uniformity)

The dose of the drug distributed per actuation of pump was within the range 88.2-103% & optimized formulation showed average drug contents per spray of $98.74 \pm 2.1631\%$. It indicated the amount of the therapeutically active ingredient delivered per metered spray from the metered dose containers & found better uniformity in term of content per spray. This procedure repeats for 20 containers. The formulation drug content per actuation is within the limit of 75% to 125% (If 2 or 3 individual content are outside the limit of 75% to 125% but individual content are within the limit of 65% to 135%).

3.4 Skin Permeation Studies

The cumulative amount (mcg/cm²) of spray release through synthetic membrane was plotted against time & found approx. linear graph. The release profile of optimized formulation demonstrated that the drug permeates cumulative is $93.3 \pm 3.1\%$ in 7hr as compare to marketed formulation $67.9 \pm 2.0\%$ cumulative release (Fig. C). It showed optimized formulation had significantly higher release of drug because of presence of lecithin, film forming agents and permeation enhancer.

Fig. C: (a) Formulation F18 (EPIC) and formulation F30 (EIPLCP) (b) Comparative release of i.e. F18, F30 and Market spray formulation



3.5 Release Kinetics

To know the drug release kinetics of optimized formulation zero order ($R^2=0.9574$), first order ($R^2=0.9588$), Higuchi ($R^2=0.9713$), Peppas plot ($R^2=0.9847$) were constructed & found *in-vitro* release profiles of drug from optimized formulations (F30) could be greatest expressed by Peppas plot as the plots showed high linearity ($R^2: 0.9847$). To verify the diffusion mechanism, the data were fitted into Higuchi equation and Korsmeyer-Peppas equation (Fig. D). The results demonstrated that the drug formulation (F30) has good linearity (0.9847) with slope values (n) >0.89 to super case II transport follows Peppas model.

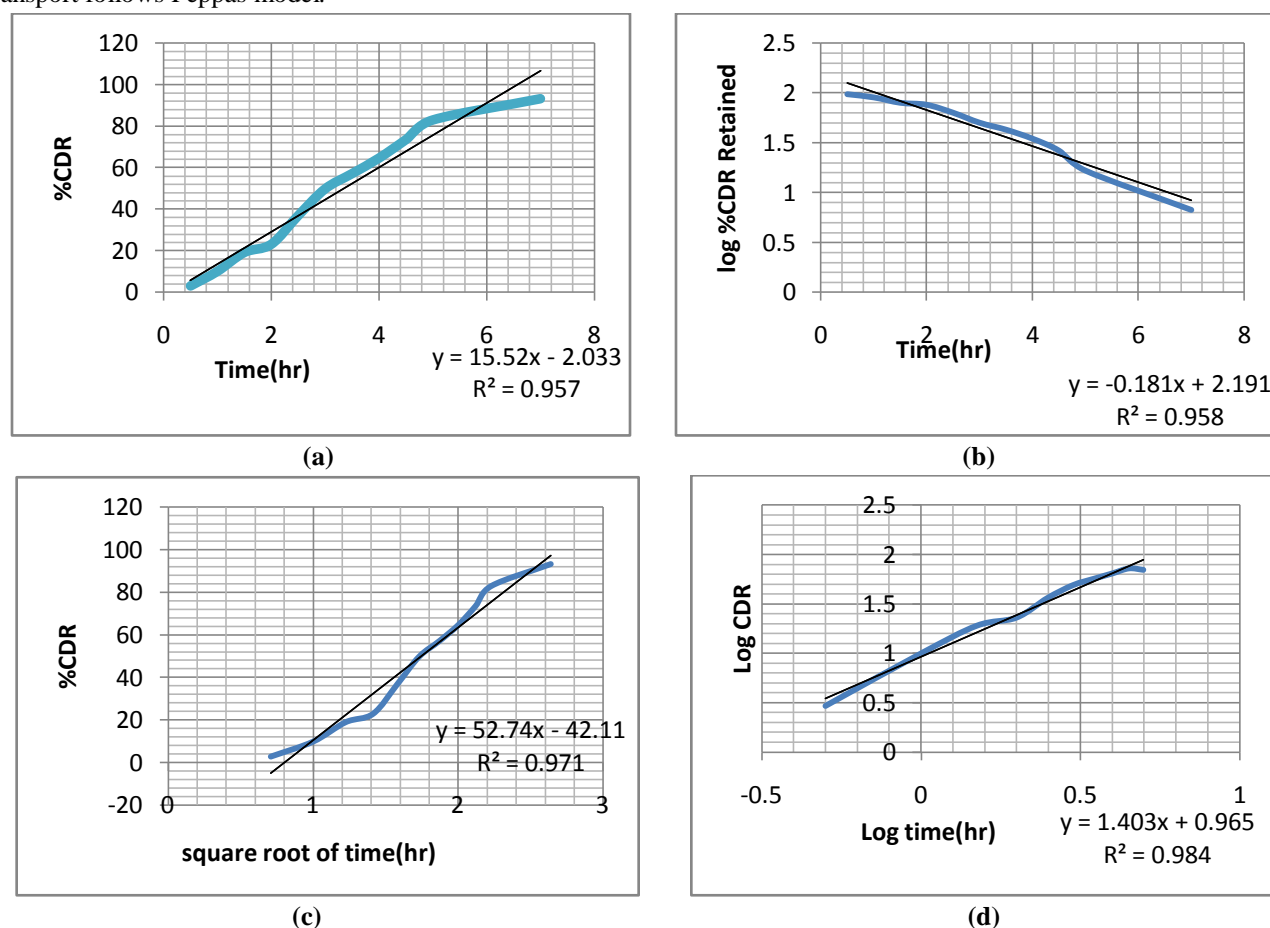


Fig. D: (a) Zero order; (b) First order; (c) Higuchi; (d) Peppas plot.

3.6 Irritation Study

The customized primary skin irritation and corrosion score was allocated from 0 to 4 based on the severity of erythema/oedema, this scoring approach given of cutaneous toxicity for a topical system. The optimized formulation's irritation on rat was at 0 level scales for erythma/edema as compared to the standard formalin solution (Fig. E). Result, showed there was no sensitivity or irritation type of reaction.

3.7 Stability

The stability is expressed as the shelf-life, wherein the product is expected to remain fit for its proposed purpose if stored properly in its stopped container. Generally shelf-life is defined as the time for the original potency of active drug to be reduced to 90%. The shelf life of non-pressurized spray (Fig. F) was found 18 months. The results (Table B and Table C) showed stability of formulation was under the acceptance criterion (acceptance condition for the assay alteration with-in 5% from its initial value) and appearance of spray product remains same. Test performed as per protocol of BP. Based on the stability data shelf-life of 18 months can be assigned to the product when stored at a temperature of 25°C.

Table B: Stability Study Results at Accelerated Stability Condition.

| Time Intervals | Parameters Study at Temperature 40±2°C/75±5%RH | | | | | | |
|----------------|---|-------------|---------------|------------------|--|---|-------------------------|
| | Description | Colour | pH (6 to 7.5) | Evaporation rate | Assay:-Each ml contains : Diclofenac Diethylamine BP 4.64 mg (Limit: NLT 4.408 mg to 4.872 mg) | Content Uniformity :- (Limit: NLT 75 % to 125%) | Cumulative drug release |
| Initial | Clear pale yellow liquid free from foreign particles. | Pale yellow | 6.01 | 9 minute | 4.562mg | 97.5±2.02% | 93.3±3.10% |
| 2 Months | Clear pale yellow liquid free from foreign particles. | Pale yellow | 6.02 | 9 minute | 4.533mg | 97.2±3.19% | 92.61±3.90% |
| 3 Months | Clear pale yellow liquid free from foreign particles. | Pale yellow | 6.03 | 8 minute | 4.519mg | 96.4±1.03% | 91.8±3.14% |
| 6 Months | Clear pale yellow liquid free from foreign particles. | Pale yellow | 6.05 | 8 minute | 4.482mg | 96.1± 2.72% | 89.8±3.50% |

Table C: Stability Study Results at Real Time Stability Condition.

| Time Intervals | Parameters Study at Temperature 30±2°C/65±5%RH | | | | | | |
|----------------|---|-------------|---------------|------------------|--|---|-------------------------|
| | Description | Colour | pH (6 to 7.5) | Evaporation rate | Assay:-Each ml contains : Diclofenac Diethylamine BP 4.64 mg (Limit: NLT 4.408 mg to 4.872 mg) | Content Uniformity :- (Limit: NLT 75 % to 125%) | Cumulative drug release |
| Initial | Clear pale yellow liquid free from foreign particles. | Pale yellow | 6.01 | 9 minute | 4.562mg | 97.5±2.02% | 93.3±3.10% |
| 3 Months | Clear pale yellow liquid free from foreign particles. | Pale yellow | 6.01 | 9 minute | 4.541mg | 97.4±3.19% | 91.85±2.20% |
| 6 Months | Clear pale yellow liquid free from foreign particles. | Pale yellow | 6.02 | 8 minute | 4.529mg | 97.4±1.93% | 90.9±4.60% |
| 9 Months | Clear pale yellow liquid free from foreign particles. | Pale yellow | 6.02 | 8 minute | 4.497mg | 96.3± 2.12% | 89.4±3.79% |
| 1 Year | Clear pale yellow liquid free from foreign particles. | Pale yellow | 6.03 | 8 minute | 4.483mg | 96.1±3.79% | 87.9±2.57% |

4. Conclusion

The non-pressurized topical spray of Diclofenac Diethylamine was formulated stable and pharmaceutically suitable liquid spray. Additionally, this study also emphasized the significance of carefully choosing specific pharmaceutical excipients and their most proper concentration in development of non-pressurized topical spray drug delivery system. The results were revealed physicochemical stable, non-irritant and non-pressurized topical spray that could deliver a considerable of formulation quantity across the skin. It was found that the compositions of topical spray F30 (Fig. F); non-occlusive films are perfectly appropriate for spraying application by means of a pump spray container.

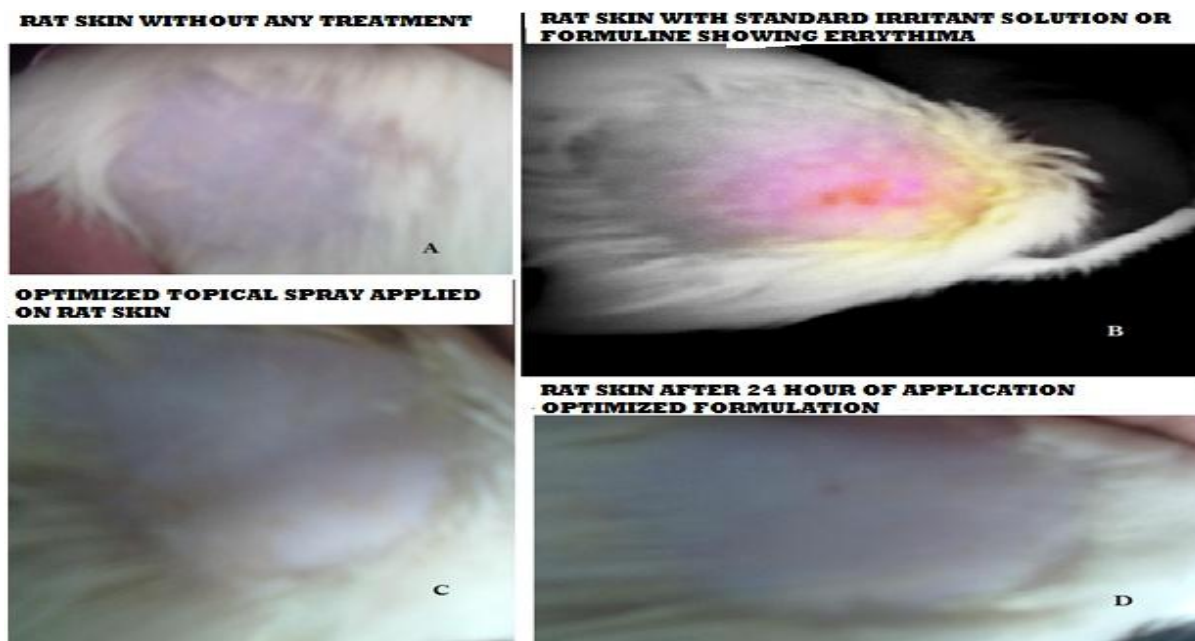


Fig. E: Rat skin irritation study; (a) Rat skin without any treatment; (b) Rat skin with treated standard irritant solution of formalin showing erythma; (c) Optimized topical spray applied on rat skin; (d) Rat skin after 24hr of application of optimized formulation.



Fig. F: Formulation batch (F30) for stability study in HDPE bottle.

Conflict of Interest

The authors have no known conflicts of interest associated with this study.

Acknowledgements

The authors wishes to thank Management of P. D. Memorial Religious Educational Association; PDM Group of Institutes(PDM College of Pharmacy), Sector: 3A, Sarai Aurangabad, Bahadurgarh, Haryana, India for financial support, and providing the facilities to carry out the research work.

References

- [1] Shepherd H.R. Aerosols: Science and technology, Interscience, Publischer Inc: Newyork, pg.119.
- [2] Palomo M., M. Ballesteros, Frustos, Analysis of diclofenac sodium derivatives, *P. J. Pharm. Anal.* 21(1999) 83-94.
- [3] Kasperek R., Swiader K., Zun M., Belniak P., Zimmer L., Dobiea E., Poleszak E., Medicine University, Lublin. 6(2011) 40-45.
- [4] Jones, D. Pharmaceuticals: Dosage form and design. Pharmaceutical solution for oral administration, *Pharm. Press. Lond.* 1(2008).
- [5] Howard C.A., Nicholas G., Popovich V.A., Pharmaceutical dosage form and drug delivery system, 6th Ed., Waverly B.I. Pvt Ltd: New Delhi, 2005, pp.456.
- [6] Paul A., Sandfrs, Hand book of aerosol technology, Van Nostrand Reinhold. pg.85, 165.
- [7] Mark, M D. Birkhoff, IvanZec, (2011) 509-524.
- [8] FDA, CDER, Guidance for industry. Nasal spray and inhalation solution, suspension and spray drug product- Chemistry, Manufacturing and controls documentation. U.S. Department of Health & Human Services, U.S, 2002.
- [9] William E.B., Pharmaceutical Dosage Form, USP30-NF25, p-378 & *Pharmacopeial Form.* 2007, 32(4), 1201.
- [10] Mary B., 2013, The concept of an aerosol can originated as early as 1790. Available from: <http://inventors.about.com/od/astartinventions/a/aerosol.htm>.
- [11] M. Geena, A. Lulla, P. Raut, *Topical spray compositions*. Island city US. U & I Pharmaceuticals Ltd.(2005)1-12.
- [12] British Pharmacopoeia, Pharm. Eur. Monograph 1807. 111,(2009) 6540-43.
- [13] Vijoya P., Shanmugam V., Lakshmi P.K., Development and optimization of novel diclofenac emulgel for topical drug delivery, *Int. J. Comp. Pharm.* 9(2011)10.
- [14] Csoka, E. Csanyi, A. Feher, G. Horvath, G. Blazso, I. Eros, In-vitro percutaneous absorption of topical dosage form: case study. *Int. J. of Pharm.* 291 (2004) 11-19.
- [15] John C., Monica C., Hang L., Loan P., , Ehab B., Hydrocortisone diffusion through synthetic membrane, Mouse skin and EpiderTM cultured skin, *Arch Drug Info.* 4(2011)10-21.
- [16] Youn, J. Jeon H., K. Nae G., Bun G. P., H.J. Seong, Diffusion properties of different compounds across various synthetic membranes using Franz-Type diffusion cells, *J. Pharm. Investigation.* 42(2012) 271-77.
- [17] Gulten K., Isik, Q. Yesim H., Sevgi A., Tamer G., Comparision of different water/oil microemulsion containing diclofenac sodium: Preparation, Characterization, Release rate and Skin irritation studies. *AAPS Pharm. Sci. Tech.* 8(4), 2007, E7.
- [18] Suresh J., Manish G., Anil, B. Vimal A., Skin irritation study of intradermal patch of chitosan containing trazodone-HCl on rat skin, *Int. J. Res. Phar. Bio. Sci.* 2(3), 2012, 1082-84.
- [19] Janos P., Gulin, WHO training workshop on pharmaceutical quality, GMP and bioequivalence with a focus on artemisinines – Stability studies. (2006) 1-61.
- [20] Swamy N., Mazhar P., Zaheer A., Formulation and evaluation of diclofenac sodium gels using sodium carboxymethyl hydroxypropyl guar and hydroxypropyl methyl cellulose, *Ind. J. Pharm. Educ. Res.* 44(4), 2010, 310-14.