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Superior Skin Penetration of Diclofenac from Dynapar QPS Plus as Compared to Diclofenac Aerosol Spray

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Background: The currently available topical diclofenac products do not provide effective penetration of diclofenac across the layers of skin. Troikaa Pharmaceuticals Ltd, has developed Dynapar QPS Plus®, a novel, topical formulation of diclofenac and compared its skin penetration with Diclofenac Aerosol Spray.

Methods: In this randomized, two way crossover study, healthy human subjects (n = 8) received single dose of either 2 ml of Dynapar QPS Plus or approximately 4 gm of marketed Diclofenac Aerosol Spray. The blood samples were drawn at pre dose and up to 24 hours post dose. The plasma concentrations of Diclofenac was measured using validated LC-MS/MS bioanalytical method.

Results: The mean Cmax after administration of Dynapar QPS Plus and Diclofenac Aerosol Spray were 102.945 ± 66.0109 and 15.885 ± 14.7750 ng/ml, respectively. Median Tmax for Dynapar QPS Plus was earlier compared to Diclofenac Aerosol Spray (7 hrs vs. 19 hrs). The mean AUC_{0-t} after administration of Dynapar QPS Plus was significantly higher as compared to Diclofenac Aerosol Spray (AUC_{0-t}: 855.289 ± 494.0262 vs. 149.707 ± 116.6317). Both the products were well tolerated and no adverse event occurred during the study.

Conclusions: The results of this study showed that Dynapar QPS Plus is safe and provides faster and more than six times higher skin penetration of diclofenac in comparison to marketed Diclofenac Aerosol Spray. Due to faster and higher penetration of diclofenac, from Dynapar QPS Plus it is best suitable option to treat pain and inflammation related to acute as well chronic musculoskeletal disorders.

Key Words: diclofenac, penetration, pharmacokinetics, skin, topical.

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INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are highly prescribed drugs for musculoskeletal pain management owing to their anti-inflammatory and analgesic properties [1]. However, orally administered NSAIDs are associated with serious and potentially fatal cardiovascular, gastrointestinal and renal complications [1-3]. Risks of these complications are increased in patients with comorbidities, the elderly, and in patients taking certain other medications including, but not limited to, antithrombotic agents, corticosteroids, and selective serotonin reuptake inhibitors. As a result, it is recommended that oral NSAIDs should either be avoided,

or used at the lowest effective dose for the shortest period of time possible [1,4].

Diclofenac is one of the routinely prescribed NSAIDs available for use in painful and inflammatory rheumatic and certain non-rheumatic conditions. Topical formulations of diclofenac are a good alternative to oral NSAIDs because systemic exposure is greatly reduced and hence the adverse event profile is favorably altered [5,6]. Further, topical diclofenac is considered as a well-tolerated, and effective first-line treatment option for knee and hand osteoarthritis (OA), especially for older patients and those who have comorbid conditions and/or risk factors for various systemic adverse events associated with oral NSAIDs, particularly at high doses and with long-term use [7].

However, the drug delivery through topical route remains a big challenge as the stratum corneum of the human skin, is known to be an effective and selective barrier to drug permeation. Skin penetration of topical formulations is dependent on liposolubility, molecular weight, partial charge of the molecule, aqueous solubility and kinetics of blood flow with reference to relative anatomic vascularity [8]. Therefore only option to enhance skin penetration of a molecule is to design an optimum drug delivery system. Several techniques have been tried to improve local drug delivery of diclofenac to deeper tissue layers. However, transdermal penetration of diclofenac has been found to be limited and variable in different formulations available in the market including creams, gels and aerosols [9-14]. It is reported that even nano-particulate based, topical drug delivery systems, cannot penetrate beyond the superficial layers of the barrier [15]. The aerosol based spray pumps have also been developed with the aim of providing higher penetration. However these aerosol based spray pump are pressurized system which uses propellants which are not much user and environment friendly [16,17]. Further, non-metered topical spray aerosols are not able to deliver accurate dosing of drugs [18]. It is also worth noting that the aerosol sprays leads to a lot of wastages of the drugs which goes into air along with propellant. At the same time the accidental inhalation of the aerosol while applying the same causes irritation of the respiratory passage.

In order to improve the penetration of diclofenac and thus increase the efficacy of topical diclofenac, Troikaa Pharmaceuticals Ltd, has developed and patented QPS (quick penetration solution) technology which provides quick and comprehensive penetration of drug through the skin. Using this technology, Troikaa has manufactured and marketed Dynapar QPS Plus which is a novel, non-aqueous, topical formulation of diclofenac diethylamine solubilised in a QPS base. Dynapar QPS is a globally patented novel drug delivery formulation which is easy to apply and after application get absorbed into the skin within 15 to 20 min. Further it is the only product which has a metered dose spray pump, thereby enabling accurate dosing of the drug. The metered dose pump functions without propellant. Hence there is no wastage and more importantly there is no possibility of the patient accidentally inhaling the formulation while applying the dose. In this study, the comparative pharmacokinetics of Dynapar QPS Plus was evaluated in healthy human subjects, which showed superior pharmacokinetics of Dynapar QPS Plus compared to Diclofenac Aerosol Spray available in the market.

MATERIALS AND METHODS

The study was carried out at Veeda Clinical Research Ltd. Ahmedabad. The study protocol was approved by Conscience Independent Ethics Committee, Ahmedabad. The study was conducted in compliance with the ICMR guidelines for National Ethical Guidelines for Biomedical and Health Research Involving Human Participants- 2017, ICH E6 (R2) 'Guidance on Good Clinical Practice', Declaration of Helsinki (Brazil, October 2013), CDSCO guideline, New Drugs and Clinical Trials Rules-2019 and DCGI guidelines and with procedures oriented to Good Laboratory Practice (OECD and Schedule L-I of D & C Rule 1945). This clinical study has been registered with Clinical Trials Registry of India (CTRI/2023/06/054540).

1. Subjects

Eight (8) healthy, adult, male human subjects, aged between 21 and 41 years & body mass index between 20.86 to 28.02 kg/m^2

participated in the study. All the subjects provided written informed consent to participate in the study prior to enrolment and were free to withdraw at any time during the study. Subjects were only included if normal laboratory values as determined by hematological tests, biochemistry, urine analysis and ECG in correlation with clinical findings. Subjects with bruises, damaged skin, eczema or wounds on the application site, or the application site inappropriate for applying the drug as per principle investigator discretion were excluded. All the subjects complied with inclusion and exclusion criteria set out in the study protocol.

2. Study design and drug administration

This was randomized, open-label, two-treatment, two-period, two-sequence, single-dose, balanced, crossover, comparative bioavailability study of Dynapar QPS Plus of Troikaa Pharmaceuticals Ltd., India with Diclofenac Aerosol Spray (available in the market) in healthy, adult, human subjects under fasting conditions. The Dynapar QPS Plus contains diclofenac diethylamine 2.32% w/v (equivalent to diclofenac sodium 2% w/v), methyl salicylate 10% w/v, menthol 5% w/v and absolute alcohol 10% v/v in topical solution (non-aqueous) base. The Diclofenac Aerosol Spray contains diclofenac diethylamine 1.16% w/v (equivalent to diclofenac sodium 1% w/v), virgin linseed oil 3% w/w, methyl salicylate 10% w/w and menthol 5% w/v. After 10 hours of overnight fasting, each human subjects received single dose of either 2 ml (equivalent to 40 mg diclofenac sodium) of test product (Dynapar QPS Plus) or approximately 4 gm (equivalent to 40 mg diclofenac sodium) of reference product (Diclofenac Aerosol Spray) via topical application as per randomization schedule in each period.

For test product administration, a topical dose of 2 ml (a total of 20 sprays; each metered dose spray delivers 0.1 ml of solution) of Dynapar QPS Plus was evenly sprayed from a distance of 6-8 inches over pre-defined area of lower back in prone position at ambient temperature as per randomization schedule. For reference product administration, topical dose of approximately 4 gm (equivalent to 40 mg diclofenac sodium) of Diclofenac Aerosol Spray was sprayed by pressing the pump mechanism keeping the nozzle from a distance of 6-8 inches over pre-defined area of lower back in prone position at ambient temperature as per randomization schedule. The solution was spread gently with a finger (wearing the gloves).

Dosing was performed by trained study personnel. The solution was applied on dry, clean, non-shaven, intact skin and covering approximately 400 cm^2 area. There was no scars or tattoos or wounds or cuts or infections or rashes or cracks or hardening at the application site or in its close vicinity.

3. Blood sampling

The pre-dose blood sample of 4.0 ml (0.00 hour) were collected within one hour prior to scheduled time of dosing in each study period. The post-dose blood samples of 4.0 ml each were drawn at 0.50, 1.00, 2.00, 3.00, 4.00, 5.00, 6.00, 7.00, 8.00, 9.00, 10.00, 12.00, 14.00, 16.00, 18.00, 20.00, 22.00 and 24.00 hours after dosing in each study period. All the blood samples were collected in pre-labeled K3EDTA vacutainer tubes. Blood samples were centrifuged at 4000 rpm for 10 minutes at 4°C for plasma separation. After separation of plasma into Cryo vials, they were stored at −78 ± 8°C until analysis.

4. Estimation of diclofenac from plasma

A validated LC-ESI-MS/MS bioanalytical method (Liquid-Liquid extraction) developed for the quantification of Diclofenac in plasma was employed for subject's sample analysis. A calibration curve extending over the range from 0.100 ng/ml to 50.000 ng/ml with a LLOQ of 0.100 ng/ml was used in subject sample analysis of Diclofenac.

5. Pharmacokinetics and statistical analysis

Pharmacokinetic and statistical analyses for plasma concentration vs. time profile of Diclofenac were performed on the data obtained from all subjects who completed both the periods of the study as per approved protocol. For Diclofenac, Pharmacokinetic

parameters C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, T_{max}, $t_{1/2}$, K_{el} and AUC_%Extrap_obs were calculated using plasma concentration vs. time profile (Actual time of sample collection) data of both investigational products in individual subjects using non-compartmental analysis in Phoenix WinNonlin® 8.3.

Descriptive statistics like no. of observations (N), mean, standard deviation (SD), minimum, median, maximum, percentage co-efficient of variation (%CV) and geometric mean were calculated for concentration profile at each time points and pharmacokinetic parameters for each formulation using Phoenix WinNonlin® Software Version 8.3. To determine the difference between the test and reference products, the ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Diclofenac were analyzed by analysis of variance (ANOVA) using PROC MIXED in SAS Software, Version 9 .4. Non-Parametric Analysis of untransformed Tmax was done using Wilcoxon Signed Rank Test. ISCV, power and %ratio and 90% CI were derived and reported.

6. Safety assessment

All subjects were assessed for safety and tolerability during the study period. This included vital signs, sitting blood pressure, body temperature, radial pulse rate, respiratory rate, local skin reactions, biochemistry and hematology.

RESULTS

1. Subject demographics and disposition

Eight subjects who met the selection criteria participated in the study. All eight subjects completed both the periods of the study. Baseline demographic data of the study populations are described in Table 1.

Table 1. Subjects demographic characteristics at screening (n = 8)

	Age (years)	Weight (kg)	Height (cm)	BMI (kg/m^2)	Gender	Race
Mean ± SD	30.25 ± 6.23	66.83 ± 8.85	166.75 ± 5.55	24.00 ± 2.66	Male	Asian
Median	30.50	66.25	169.00	24.14		

2. Pharmacokinetics

Mean plasma diclofenac concentration vs. time profile for both treatments is shown in Fig. 1.

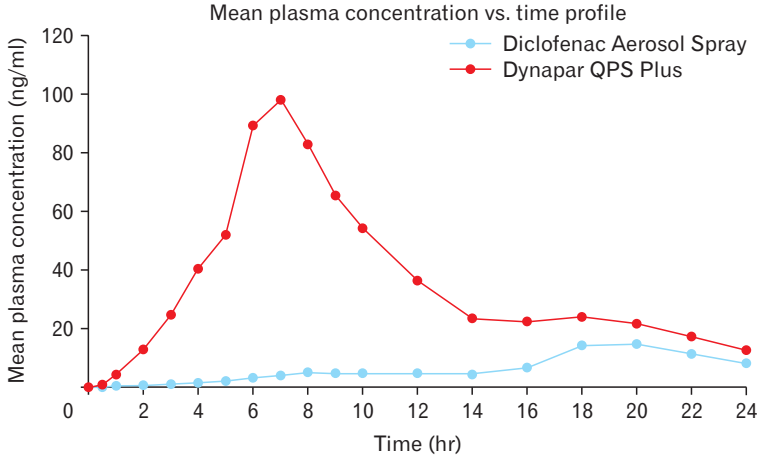

Fig. 1. Mean plasma concentration vs. time profile of diclofenac after topical application of Diclofenac Aerosol Spray and Dynapar QPS Plus in healthy human subjects.

The maximum plasma concentration (C_{max}) of diclofenac after administration of Dynapar QPS Plus and Diclofenac Aerosol Spray were 102.945 ± 66.0109 and 15.885 ± 14.7750 ng/ml, respectively (Table 2, Fig. 2). The test/reference ratio of geometric least squares means for Cmax was 701.17% indicating more than 7 fold higher Cmax with Dynapar QPS Plus compared to Diclofenac Aerosol Spray (Table 3).

Median time to reach maximum plasma concentration (T_{max}) for Dynapar QPS Plus was earlier compared to Diclofenac Aerosol Spray (7 hrs vs. 19 hrs) (Table 2). The statistical significant difference between median of Tmax of both the treatments were evaluated using non-parametric Wilcoxon signed rank test for Diclofenac. The P-value was observed as 0.0078 (< 0.05), which is statistical significant. So, these results indicates faster absorption of diclofenac from Dynapar QPS Plus compared to Diclofenac Aerosol Spray.

The mean AUC_{0-t} after administration of Dynapar QPS Plus was significantly higher as compared to Diclofenac Aerosol Spray (AUC_{0-t}:

Table 2. The mean pharmacokinetic parameters of diclofenac estimated for the reference (Diclofenac Aerosol Spray) and test (Dynapar QPS Plus) formulation (n = 8)

PK parameter	Reference (mean ± SD)	Test (mean ± SD)
C_{max} (ng/ml)	15.885 ± 14.7750	102.945 ± 66.0109
AUC_{0-t} (ng x hr/ml)	149.707 ± 116.6317	855.289 ± 494.0262
AUC_{0-inf} (ng x hr/ml)	237.195 ± 46.8059	957.751 ± 476.3460
$^{\#}T_{max}$ (hr)	19.000 (8.00-22.00)	7.000 (6.00-10.00)
$t_{1/2}$ (hr)	6.405 ± 3.4826	6.476 ± 3.8495
K_{el} (1/hr)	0.131 ± 0.0648	0.133 ± 0.0532

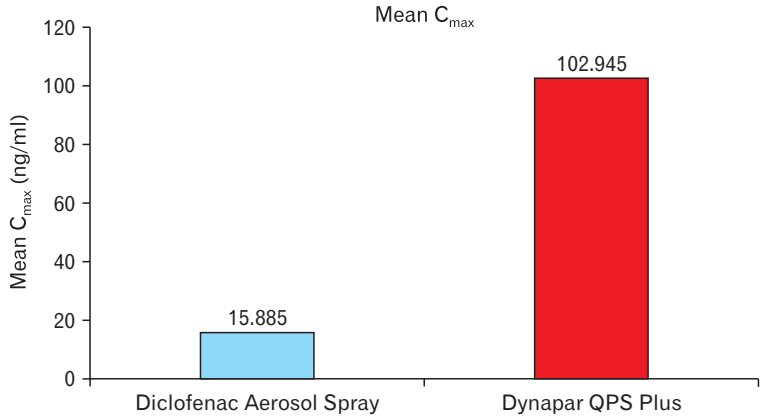

Fig. 2. Mean maximum plasma concentration (C_{max}) of diclofenac after topical application of Diclofenac Aerosol Spray and Dynapar QPS Plus in healthy human subjects.

Table 3. The statistical analysis for primary pharmacokinetic parameters of diclofenac

PK parameters (units)	Geometric least squares means ratio (T/R) (%)	Intra-subject CV (%)	90% confidence interval	Power (%)
C_{max} (ng/ml)	701.17	34.68	505.36-972.83%	27.93
AUC_{0-t} (hr*ng/ml)	616.50	17.08	522.85-726.91%	74.16

T/R ratio: test/reference ratio; R: reference product (Diclofenac Aerosol Spray); T: test product (Dynapar QPS Plus).

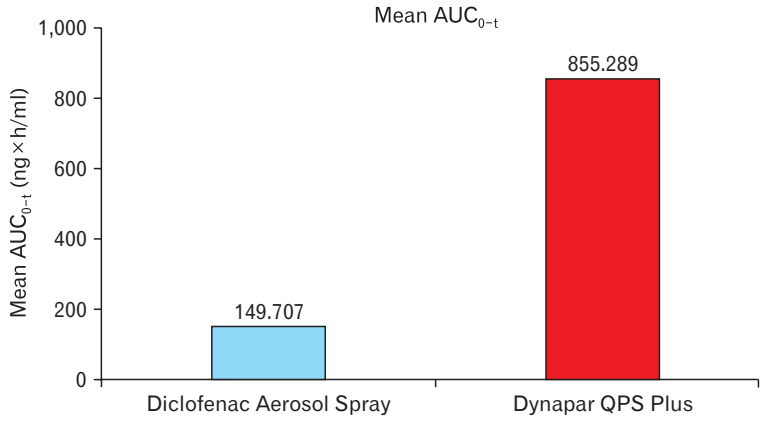

Fig. 3. Mean area under the curve (AUC_{0-t}) of diclofenac after topical application of Diclofenac Aerosol Spray and Dynapar QPS Plus in healthy human subjects.

855.289 ± 494.0262 vs. 149.707 ± 116.6317 ng.h/ml) (Table 2). The % test/reference ratio of geometric least square means for AUC_{0-t} was 616.50% indicating more than 6 fold higher exposure (Table 3, Fig. 3). The mean $AUC_{0-\infty}$ after administration of Dynapar QPS Plus was significantly higher as compared to Diclofenac Aerosol Spray ($AUC_{0-\infty}$: 957.751 ± 476.3460 vs. 237.195 ± 46.8059 ng.h/ml) (Table 2).

3. Safety assessment

Clinical examination (including physical and systemic examination), vital signs examination, laboratory safety assessment, skin irritation assessment, and well-being assessment were recorded. Based on these safety assessments, all values and reports of all subjects was found within normal limit or as clinically not significant. No death, no adverse event or any other associated serious adverse event occurred during the conduct of the study. Hence, both the products were well tolerated by the subjects.

DISCUSSION

Diclofenac is one of the routinely prescribed NSAIDs for the management of painful and inflammatory rheumatic and certain non-rheumatic conditions. Topical formulations of diclofenac are a good alternative to oral NSAIDs because systemic exposure is greatly reduced and hence the adverse event profile is favorably altered. Most of the available topical products are not able to penetrate through the skin effectively and thereby provide limited benefit of this approach [9-14]. We have developed the novel Quick Penetration Solution (QPS) based technology for effective skin penetration. Dynapar QPS Plus is based on this technological platform, where diclofenac, methyl salicylate and menthol was dissolved in QPS base. Dynapar QPS is a globally patented novel drug delivery formulation which is easy to apply and after application get absorbed into the skin within 15 to 20 min. Further it is the only product which has a metered dose spray pump, thereby enabling accurate dosing of the drug. In this randomized, single dose and open label study, comparative bioavailability of the novel topical diclofenac spray (Dynapar QPS Plus) was evaluated with Diclofenac Aerosol Spray available in the market. The results of this study showed that mean time to reach C_{max} (T_{max}) for Dynapar QPS Plus was much earlier compared to Diclofenac Aerosol Spray (7 hrs vs. 19 hrs). The % test/reference ratios of geometric least square means of C_{max} and AUC_{0-t} were 701.17 and 616.50% respectively. These indicate that more than 7 and 6 times higher C_{max} and AUC respectively for Dynapar QPS Plus in comparison to Diclofenac Aerosol Spray. So there was higher and faster absorption of the diclofenac from Dynapar QPS Plus compared to Diclofenac Aerosol Spray. This higher penetration validates the advantage of novel

QPS technology of Troikaa against aerosol sprays.

The penetration of diclofenac form Dynapar QPS Plus is superior compared to globally approved topical diclofenac products. In a human pharmacokinetics study of diclofenac sodium 2% solution (Pennsaid marketed in the USA) with BID dosing (40 mg single dose) the Cmax of 12.16 ng/ml and AUC_{0-12} of 77.27 ng*h/ml was observed on day 1. Our data indicates more than 8 fold higher Cmax and more than 11 fold higher AUC observed with Dynapar QPS Plus as compared to Pennsaid 2% solution [19]. Similarly, topical application of diclofenac diethylamine 2.32% gel (Voltarol Emulgel marketed in the Europe) with BID dosing (40 mg single dose), AUC_{0-24} of 21.7 ± 15.2 ng*h/ml of was observed. Comparing with AUC observed in this study, there was 39 fold higher AUC was observed with Dynapar QPS Plus as compared to Voltarol Emulgel 2.32% gel [20]. The small sample size used in the study can be considered as limitation of this study. However looking at the very high difference in the penetration between both the product and the previous experience of superior penetration and efficacy with use of QPS technology, the results would have been similar, had the study been conducted on higher number of subjects.

Dynapar QPS Plus is non-pressurized spray dispensing system which does not require use of propellant so safer than aerosol spray pumps [16,17]. Dynapar QPS Plus container has metered valve for delivering exact quantities of product at each discharge. As the delivery of medicine from the Dynapar QPS Plus pump is well directed to the affected areas due to its unique pump design, the wastage of medicine is minimal compared to aerosol based spray.

In contrast, non-metered topical spray aerosols are not able to deliver accurate dosing of drugs due to effects of various parameters on dispensing efficiency like temperature of the aerosol product, target distance and non-volatile content [18]. It is also worth noting that the aerosol sprays leads to a lot of wastages of the drugs which goes into air along with propellant. This also can lead to accidental inhalation of the aerosol resulting in respiratory distress.

Using this QPS technology Troikaa earlier had developed and marketed Dynapar QPS® (topical spray containing diclofenac diethylamine 4.64% w/v), which has proven superior skin penetration in human bioavailability study [21], microdialysis study [22] and in scintigraphy study [23]. Further Dynapar QPS provided superior efficacy compared to diclofenac gel without compromising safety in management of acute musculoskeletal pain as compared to diclofenac gel available in the market [24,25]. So both the product based on this technology provides safe and effective option for treating pain and inflammation related musculoskeletal pathologies.

CONCLUSION

The results of this study showed Dynapar QPS Plus is safe and provides faster and more than six times higher skin penetration of diclofenac in comparison to marketed Diclofenac Aerosol Spray. Due to faster and higher penetration of diclofenac, from Dynapar QPS Plus, it is best suitable option to treat pain and inflammation related to acute as well chronic musculoskeletal disorders.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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