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RESEARCH PAPER

FORMULATION AND EVALUATION OF LEVOCETIRIZINE TOPICAL GEL

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Levocetirizine Dihydrochloride (LTZ) is a second-generation histamine antagonist used to treat various allergic symptoms and skin disorders like hives including itching, rashes and dermatitis. LTZ causes drowsiness and hepatotoxicity when administered orally. The aim of this research was to develop and evaluate topical gel which can avoid systemic side effects. Hence, the gel was formulated using different ratios/grades of Carbopol as primary gelling agents and different ratios of cellulose derivatives as combination polymers. Total thirteen (13) formulations were developed and characterized for physical evaluation and other attributes such as % drug content, pH, spreadability, extrudability, homogeneity, consistency, in-vitro drug release, viscosity, and skin irritation. Fourier Transform Infrared Spectroscopy (FTIR) and Differential Scanning Calorimetry (DSC) studies revealed the drug purity and drug-excipients compatibility. The formulations which did not comply with the physical appearance and homogeneity tests were rejected. Three formulations which showed best results in homogeneity test were evaluated for viscosity and in-vitro drug release study. The formulation F6 which showed maximum % drug release was subjected to skin irritation study using human volunteers and finally for the stability study at accelerated storage conditions for three months. The F6 formulation showed good quality attributes and can be further recommended to be evaluated for ex-vivo permeation and topical bioavailability. It can be concluded that the gel formulation of LTZ using combination of gelling agent and polymer displayed potential to be developed as novel topical formulation of LTZ with possible prevention of systemic side effects.

Key words: Topical gel, Levocetirizine dihydrochloride, Gelling agents, Polymers, Carbopol.

INTRODUCTION

Topical preparations are used for the localized effects produced either at the site of their application by virtue of drug penetration into the underlying layers of skin or by diffusing through the skin through hair follicles, sweat glands or sebaceous glands followed by permeation through the multiple lipid bilayers. Topical medications can be applied to the skin, surface of the eye or used nasally, vaginally or rectally. Most topical medicines are intended for use on the skin. There are three layers of skin *i.e.* epidermis (outermost layer), dermis (middle layer) and hypodermis (innermost layer) [1-5]. Topical gels are non-toxic, less greasy, easily applicable to the target area, avoid first-pass metabolism, easily washable [6]; hence provides better patient compliance.

LTZ is a second-generation histamine antagonist used to treat various allergic symptoms and also to treat symptoms of skin disorders like hives including itching and rashes. It acts as an inverse agonist that selectively inhibits histamine H_1 receptors. This in turn prevents the release of

other allergy-causing chemicals and increases the blood supply to the area, providing relief from typical symptoms of hay fever or allergy [2]. Till date, topical formulation for LTZ is not available in market. So, aim of the present research was to develop and evaluate topical gel formulation of LTZ to avoid systemic side effects.

MATERIALS AND METHODS

LTZ was received as a gift sample from Maps Laboratories Pvt. Limited, Rajkot, India. Hydroxypropyl methyl cellulose (HPMC) was received as a gift sample from Colorcon Asia Pvt. Ltd., Goa. Carbopol 971P and hydroxyethyl cellulose (HEC) were received as gift samples from Lubrizol, USA and Ashland Industries, Netherlands respectively. Carbopol 934P and triethanolamine were received as gift from MMRDC, Modipuram (Manufacturers - Lubrizol, USA and Merck Ltd.). All other chemicals, solvents and reagents were of analytical grade and purchased from Delhi.

Pre-formulation studies:

Pre-formulation studies for drug substance were performed which includes Identification by FTIR and its comparison with reference spectrum given in Indian Pharmacopoeia 2018 (**Figure 1a**, **1b**), solubility studies, melting point, partition coefficient, absorption maximum, thermal studies at different temperatures like room temperature (RT), 40°C, 50°C (each condition for one month), and 80°C (for 72 h) etc.

Drug-excipients compatibility studies were performed by mixing drug substance LTZ and excipients (*i.e.* Carbopol 934P and 971P, HPMC, HEC, Glycerin, Propylene Glycol and EDTA) individually and blend of all excipients in 1:1 ratio and after 15 days, subjected to FTIR and DSC studies [3, 6].

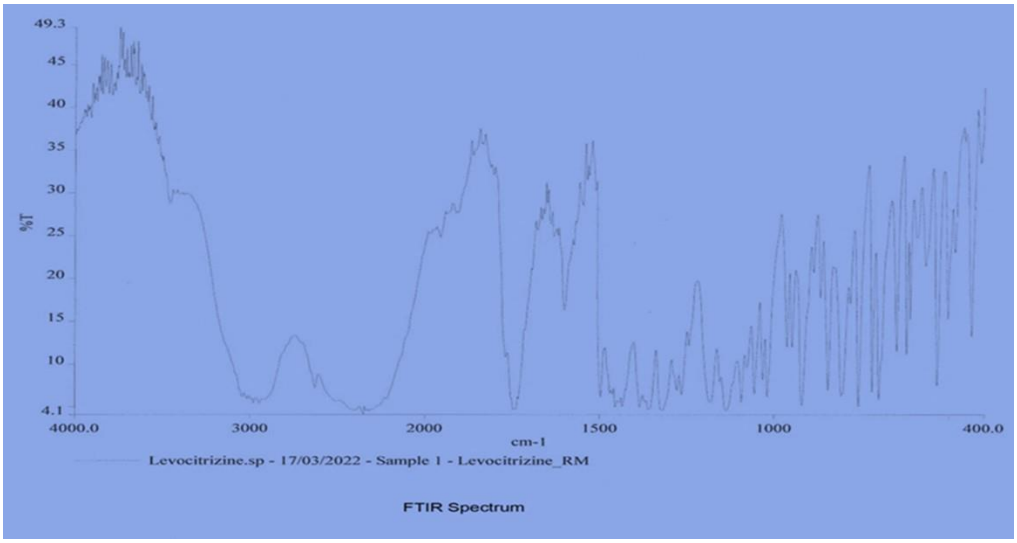

Figure 1a. FTIR spectrum of pure sample LTZ

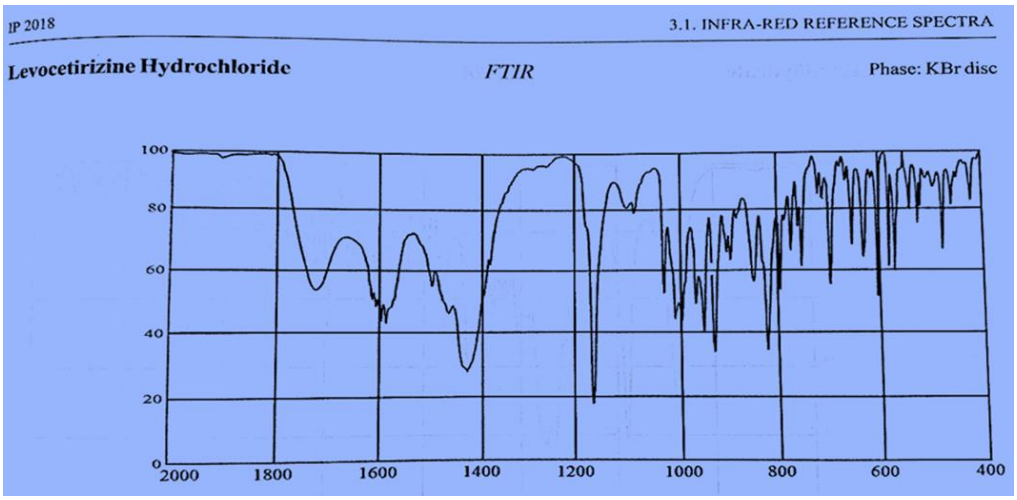

Figure 1b. FTIR reference spectrum of LTZ (IP 2018)

Gel formulation:

Thirteen formulations were developed using different gelling agents, polymers, penetration enhancer and stabilizers, as shown in **Table 1**. Total 100 g of gel was prepared for each formulation by varying the gelling agents and polymers used and their proportion. The gel was formulated by preparing two phases *i.e.* Polymer phase and Drug phase. Polymer phase contained Carbopol 934P/971P and other polymers as per different formulations (**Table 1**) and drug phase contained drug substance dissolved in purified water and glycerin (where applicable).

pH of both phases were adjusted to 6.8 individually. Drug phase was then, mixed to the polymer phase slowly drop by drop with continuous stirring and pH of the resulting gel was finally adjusted to 6.8. Final weight of prepared gel was made up to 100 g by adding purified water [7-9].

Table 1. Composition of topical gel formulations

Ingredients	Formulation code												
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
Levocetirizine HCl (g)	5	5	5	5	5	5	5	5	5	5	5	5	5
Carbopol 934P(g)	1	1	2	2	-	2	1	1	1	1	2	1	1
Carbopol 971P (g)	-	-	-	-	1	-	-	-	-	-	-	-	-
HPMC (g)	1	2	1	1	1	1	1	2	1	2	1	2	1
HEC (g)	-	-	-	-	-	-	-	-	1	1	1	-	-
EDTA (g)	0.2	0.2	0.2	-	-	-	-	-	-	-	-	-	-
Ethyl alcohol (g)	-	-	-	-	-	-	-	-	-	-	-	25	25
Propylene glycol (g)	-	-	-	-	5	10	10	10	-	-	-	-	-
Glycerine (g)	-	-	-	-	25	20	20	20	30	30	30	-	-
Triethanolamine (g)	*q.s.*	*q.s.*	*q.s.*	*q.s.*	*q.s.*	*q.s.*	*q.s.*	*q.s.*	*q.s.*	*q.s.*	*q.s.*	*q.s.*	*q.s.*
Purified water (g) upto	100	100	100	100	100	100	100	100	100	100	100	100	100

Evaluation of gel:

All the developed formulations were subjected to the physicochemical characterization. Formulations exhibiting unacceptable results during visual examination (05 number) were discarded and rest were proceeded for further characterization parameters such as % drug content, pH, spreadability, extrudability, homogeneity, consistency. Further, selected formulations based on homogeneity were subjected to *in-vitro* drug release study and viscosity test [10-16]. Finally, the best *in-vitro* formulation was further evaluated for skin irritation and stability studies at accelerated storage conditions of 40±2°C temp. / 75±5% RH for 3 months [17-22].

Visual examination of gels:

The formulated gels were stored for 2 weeks at room temperature and then visually examined for clarity, colour, transparency and any grittiness.

Drug content determination:

Percent (%) drug content was determined for eight formulations using the UV-Visible spectrophotometer at a wavelength of 231 nm by preparing 10 ppm solution in methanol.

pH determination:

20 g of gel formulation was transferred to a 50 ml beaker and pH was measured using a digital pH meter at 25°C.

Spreadability test:

Spreadability of gel was measured by spreading 0.5 g of vitro gel on a circle of 2 cm diameter pre-marked on a glass slide and then a second glass slide was employed over it. Half kg of weight was permitted to rest on the upper glass slide for 5 minutes. Diameter of circle after spreading of gel was determined to calculate spreadability.

Extrudability test:

20 g of prepared gel was filled in aluminium collapsible tubes (20 g, with a tip opening of 5 mm) and was sealed with the help of a crimping machine. Weight required to extrude 0.5 cm ribbon of gel in 10 sec was determined.

Consistency test:

The consistency of prepared gels was determined by dropping a cone attached to a holder rod from a fixed height of 10 cm such that it falls on the centre of the gel surface filled in a beaker. The cone's penetration was measured from the gel's surface to the tip of the cone inside

the gel. The distance moved by the cone in 10 sec was recorded and used to determine the consistency.

Homogeneity test:
The developed gel formulations were tested for homogeneity/sedimentation test by the visual inspection against light from all the sides after the gels have been set in the containers and left undisturbed at room temperature for 15 days. Gels were tested for their physical appearance and presence of any aggregates/lumps, if any and recorded.

Viscosity test:
Viscosity (in cps) of gel formulations was determined by using the Brookfield Digital Viscometer attached with LV-5 (65) spindle. The spindle was rotated at different speeds of 10, 20, 40 and 60 rpm after allowing the gel samples to settle for 30 min at the temperature (25±1°C) before the measurements were taken.

In-vitro drug release study:
In-vitro drug release study was performed using Franz diffusion cell apparatus (Meditech Technologies India Pvt. Ltd.). Egg membrane was used as a semi-permeable membrane. Gel was placed on the egg membrane (on donor compartment of apparatus). The holder containing egg membrane and drug product was placed on the receiver compartment of the cell containing 100 ml of phosphate buffer solution of pH 6.8 as dissolution medium and 37±0.5°C temperature. The samples (5 ml) were withdrawn at 30 min interval up to 4 h, diluted if required and and analyzed for the drug content using UV-Visible spectrophotometer at 231 nm and the amount of drug released from gel was calculated. After each sample withdrawal, receptor phase was replenished with an equal volume of fresh medium

Skin irritation study:
Ten human volunteers (with prior consent) of different age groups and gender were selected for skin irritation study using the selected best formulation by applying gel on the area of 2 inch [2] to the back side of the hand and examined for three consecutive days for the presence of any irritation/lesions.

Stability study:
Stability study of selected formulation was carried out as per the International Council for Harmonization (ICH) guidelines Q1A (R2) for three months to verify the quality of drug product under the influence of temperature and relative humidity at accelerated storage conditions of 40±2°C temp. / 75±5% RH and tested at an interval of 1, 2 and 3 months to determine any significant change in physical appearance, pH and % drug content [18].

RESULTS AND DISCUSSION

Pre-formulation studies:
Melting range of drug substance found between 215-220°C. LTZ was found to be freely soluble in purified water, soluble in methanol and phosphate buffer pH 6.8. Thermal studies revealed that drug substance was stable at accelerated storage conditions.

Drug-excipient compatibility studies:
No significant change in the peak behaviour of functional groups of drug substance was observed in presence of excipients in 1:1 ratio when examined using FTIR (**Figure 2**). Further, DSC spectra did not show any physical/chemical interaction in drug–excipient mixture in 1:1 ratio (**Figures 3, 4**).

Visual examination:
Eight out of thirteen developed formulations were found to be clear, transparent and homogeneous, when examined visually.

% Drug content:
Results obtained revealed that % drug content of eight formulations varied from 96.67% to 98.84% *w/w* for formulations F9 and F6.

pH:
Results obtained concluded that pH value of all formulations varied from 6.3 to 6.9 which found compatible with the pH of the skin.

Spreadability:
Spreadability of all eight formulations was found to be between 25.65-35.54 with minimum for F9 and maximum for F6 formulation respectively, indicating that there was not much difference in the spreadability among the formulations.

Extrudability test:
Extrudability of eight formulations was found between 4.9 to 5.7, indicating that there was not much difference amongst extrudability of all the formulations. The higher the extrudability, the better is the gel.

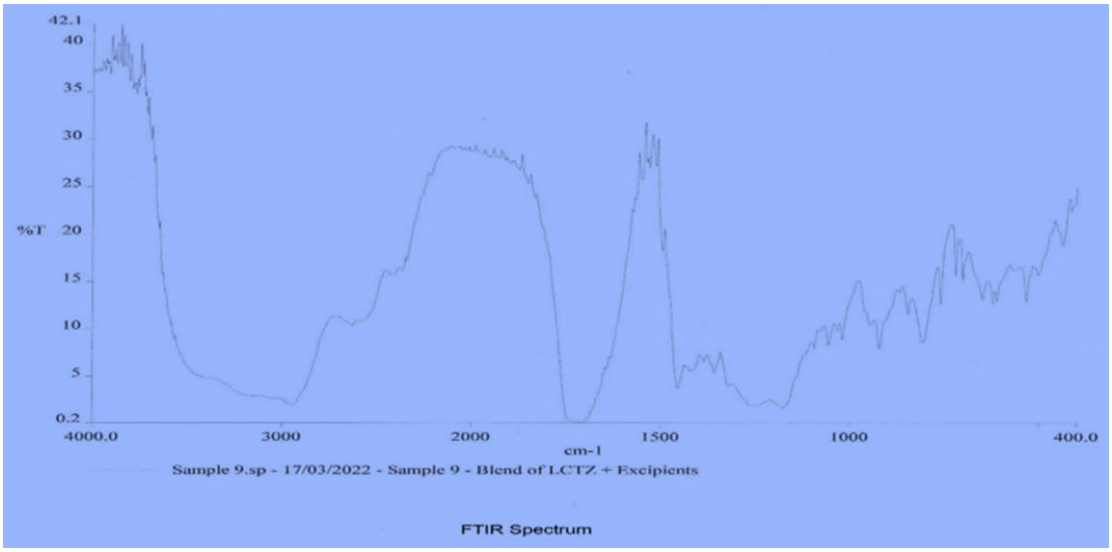

Fig. 2. FTIR spectra for blend of LTZ + excipients*

(*Excipients include Carbopol 934P, Carbopol 971P, HPMC, HEC, Glycerin, Propylene Glycol and EDTA)

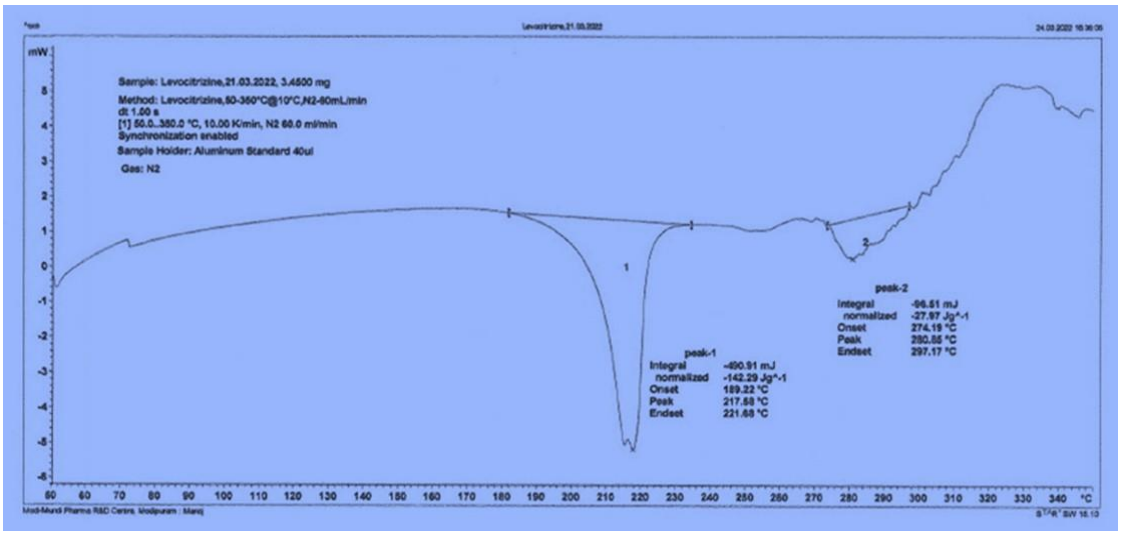

Fig. 3. DSC spectrum of pure LTZ

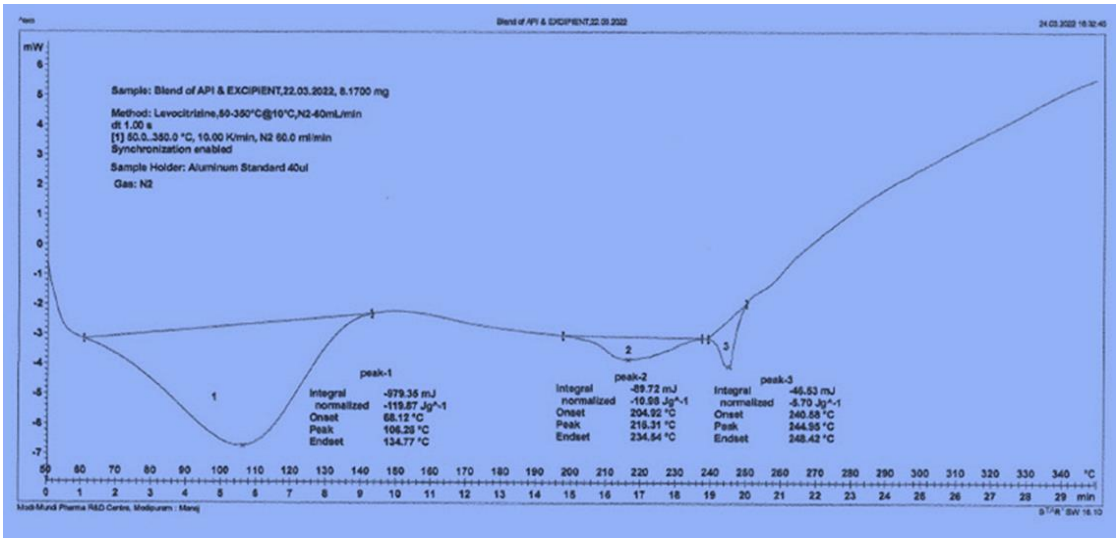

Fig. 4. DSC spectrum of blend LTZ + excipients*

(*Excipients include Carbopol 934P, Carbopol 971P, HPMC, HEC, Glycerin, Propylene Glycol and EDTA)

Consistency:
The consistency is inversely proportional to the distance traveled by falling cone and considered in the range from 0-10. Consistency in terms of distance travel by cone was observed to be 4-6 mm of all developed gels.

Homogeneity test:
Homogeneity test revealed that the three formulations F6, F7 and F8 were homogeneous with no sedimentation orlumps. However, aggregates were observed in the formulation F4, F9, F10 and F11, hence they were not evaluated further.

Viscosity of gel:
Viscosity of F6, F7 and F8 was determined and found between 60,250 to 9896 cP. Order of viscosity of three formulations were F6 > F8 > F7. (**Table 2**, **Figure 5**).

Table 2. Observation for viscosity test

Spindle Speed (rpm)	Formulation code		
	F6	F7	F8
	Viscosity (cP)		
10	60250	52874	58236
20	42745	37623	40853
40	25096	21732	23490
60	10832	9896	10105

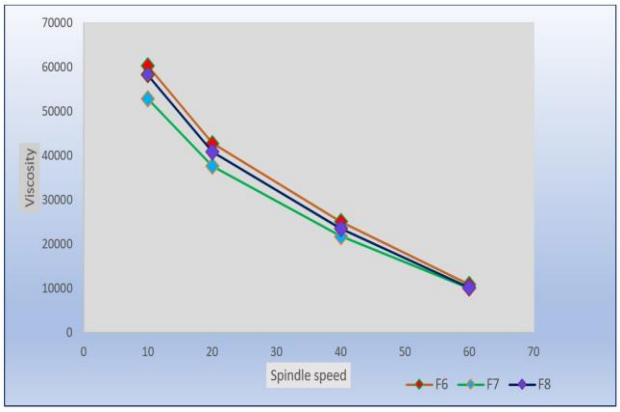

Fig. 5. Viscosity of selected formulations F6, F7 and F8

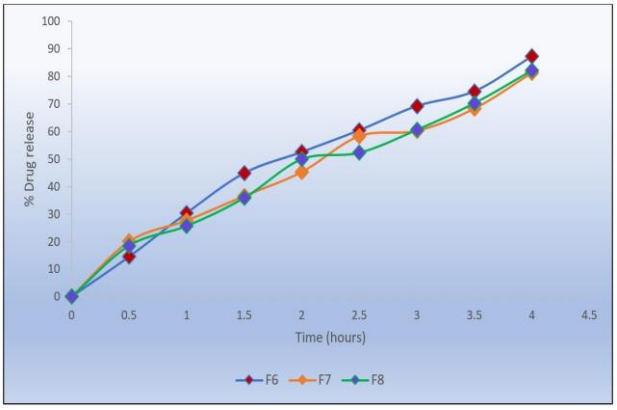

Fig. 6. Comparative *in-vitro* drug release profiles of formulations F6, F7 and F8

In-vitro drug release test:
In-vitro drug release of F6, F7 and F8 revealed that the % drug released was in the range of 81.28 to 87.26% *w/w*. It was found that the formulation F6 containing Carbopol 934P and HPMC in 2:1 ratio showed maximum % drug release at 4 h than rest two formulations having 1:1 (F7) and 1:2 (F8) ratio of Carbopol 934P and HPMC respectively.
Order of % drug release in the three formulations was F6 > F8 > F7. The comparative % drug release profiles of all three formulations is shown in **Figure 6**.

Skin irritation study:
During skin irritation study using F6, no volunteer out of selected volunteers (ten) complained of any irritation on the area of application of the skin.

Stability study:
Stability study of F6 formulation was carried out at accelerated storage conditions (40±2°C temperature / 75±5% RH) for three months and no significant change observed in physical appearance, pH and % drug content (97.14% *w/w* from the initial value of 98.84% *w/w*) after three months. Hence, it can be suggested that F6 gel formulation has potential to be developed as safe, effective, stable topical formulation of LTZ.

CONCLUSION

The study results concluded that the LTZ topical gel prepared with combination of Carbopol 934P and HPMC (2:1) displayed acceptable physical and chemical characteristics and could be further recommended to be evaluated for *ex vivo* studies and topical bioavailability. The gel formulation developed using combined gelling

agent and polymer appears to be safe, stable and effective with potential of developing as novel topical formulation of LTZ with minimal systemic side effects.

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