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Original Article

Preparation and evaluation of an Emulgel of Hydroxyzine hydrochloride

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ABSTRACT: Hydroxyzine hydrochloride is effective in the treatment of urticaria and other allergic skin disorders. Hydroxyzine hydrochloride emulgel potentially enhances drug penetration into the stratum corneum and localizes the drug within the dermo-epidermal layers. Emulgel was formulated by first preparing the emulsion using fixed oils and non-ionic surfactants, and then incorporated into a gel base. Emulsions were primarily optimized using non-ionic surfactants, Span 60 and Tween 20 and gel was optimized using Carbopol 940, HPMC K100M and xanthan gum. These optimized formulations were studied for *in vitro* drug release studies followed by ex vivo, skin irritation and stability studies. The optimized o/w emulgel was compared with the w/o emulgel which showed the in vitro release of 76.7% and ex vivo studies showed 42.3% release at the end of 8th hr. The *ex vivo* release of optimized HESX (o/w emulgel) formulation was compared with the HESX1 (w/o emulgel) formulation which showed the release of 53% and 42.3% release respectively. The emulgel formulation HESX showed irritation potential of '0', thus proving to be non-irritant. Hence, it can be concluded that o/w emulgel formulation of hydroxyzine hydrochloride showed better release than the w/o emulgel.

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INTRODUCTION

When a gel and emulsion are used in combined form it is referred as Emulgel. Emulgels have emerged as promising drug delivery system for the delivery of hydrophobic drugs. Emulgels are a relatively newer class of dosage forms created by entrapment of large amounts of aqueous or hydro alcoholic liquid in a network of colloidal solid particles, which may consist of inorganic substances, such as aluminum salts or organic polymers of natural or synthetic origin [1-6]. Emulgels have a higher aqueous component which permits greater dissolution of drugs, and permit easy migration of the drug through a vehicle that is essentially a liquid [7-11].

MATERIALS AND METHODS

The materials used include: Hydroxyzine Hydrochloride(HHCL) (Symed Labs Ltd., India), Carbopol 940, HPMC K4M, K15M, K100M (Coral Pharma Chem. Ltd., India), Tweens 20,80, Spans 20,40,60,80, Propylene glycol (S.D. Fine Chemicals Ltd., India), Coconut oil (Marico Ltd., India), Sesame oil (V.V.V and Sons edible oils Ltd., India), Olive oil (Aceites Agro Sevilla, Spain). All the other materials used were of pharmaceutical grade.

Compatibility between drug and excipients [12]

Interactions between drug and excipients were studied by Fourier Transform Infra-Red (FTIR) Spectroscopy to check compatibility of drug and excipients. Infrared spectrum of HHCL and excipients was determined on FTIR (8400 S Shimadzu) using potassium bromide (KBr) dispersion method. The base line correction was done using dried KBr. Then the spectrum of dried mixture of drug and potassium bromide was run followed by drug and excipients in the wavelength region between 4000 and 400cm.

Preparation of Emulsions

Oil phase was prepared by adding lipophilic surfactant (Spans) to the oil (olive oil, coconut oil, sesame oil) and the aqueous phase was prepared by adding hydrophilic surfactant (Tweens) to water and then heated to 65-70^{O}C. Oil in water emulsion was prepared by the addition of oil phase to the aqueous phase with continuous stirring.

Table 1: Formulation of o/w and w/o emulsion of HHCL

Ingredients (%w/w)	HEO	HEC	HES	HES1
Drug	3.6	3.6	3.6	3.6
Olive oil	6	-	-	-
Coconut oil	-	6	-	-
Sesame oil	-	-	6	q.s
Span 60	3.23	2.9	3.23	-
Span 80	-	-	-	2.5
Tween 20	0.76	1.1	0.76	-
Distilled water	q.s	q.s	q.s	2

HEO, HES, HEC indicate emulsions formulated with olive oil, sesame oil, and coconut oil respectively. HES1 is a w/o emulsion.

Evaluation of optimized emulsion

The optimized emulsion was evaluated by performing particle size analysis, dilution test, dye solubility test, conductivity and assay.

In vitro drug release

In vitro drug release studies were carried out using modified Franz diffusion (FD) cell with 200 ml of the release medium, PBS pH 7.4, and maintained at 37ºC±0.5ºC. The whole assembly is kept on magnetic stirrer and solution was stirred continuously using magnetic bead, at 350 rpm and aliquots each of 5 ml were withdrawn from the release medium at specified time intervals. The withdrawn samples were replaced by equal volumes of fresh release medium. The samples were assayed spectro-photometrically at λ_{max} of 230nm and the concentration of the drug was determined from the calibration curve.

Preparation of Gels [14]

Three different gels of HPMC K100M, Carbopol 940, and Xanthan Gum were prepared by soaking them for 24hrs then they are stirred well and finally the pH was adjusted.

Table 2: Formulation of gels

Ingredients (%w/w)	HGC	HGH	HGX
Drug	3.6	3.6	3.6
Carbopol 940	1	-	-
HPMC K100M	-	1	-
Xanthan gum	-	-	2
Triethanolamine	0.5	-	-
Distilled water	q.s	q.s	q.s

HGC, HGX, HGH indicate gels formulated with Carbopol 940, xanthan gum, and HPMC K100M respectively.

Evaluation of optimized gel

Physical appearance and Homogeneity

The physical appearance and homogeneity of the prepared gels were tested by visual observations after the gels have been set in the container. They were tested for their appearance and presence of any aggregates.

Clarity

The clarity of various formulations was determined by visual inspection under black and white background and it was graded as follows: turbid: +, clear: ++, very clear (glassy): +++.

Measurement of pH

The pH of various gel formulations was determined by using digital pH meter. One gram of gel was dissolved in 100 ml distilled water and stored for two hours. The measurement of pH of each formulation was done in triplicate and average values were calculated.

Viscosity study

Viscosity of prepared gels was determined by Brookfield programmable viscometer. The spindle number 64 was rotated at 50rpm. Samples of the gels were allowed to settle over 30 minutes at the 25ºC before measurements were taken.

Spreadability

The spreadability of the gel formulations was determined by measuring the spreading diameter of 1g of the gel between 20X20 cm glass plates after 1min.The mass of the upper plate was standardized at 10g. The spreadability was calculated by using the formula [15].

$$S = M \times L / T$$

Where S is the spreadability, M is the weight in the pan (tied to the upper slide), L is the length moved by the glass slide and T represents the time in seconds taken to separate the slide completely.

Extrudability

Gels with high consistency may not extrude from the tube whereas, low viscous gels may flow quickly, and hence suitable consistency is required in order to extrude the gel from the tube. The formulations were filled into collapsible aluminum tubes. The tubes were pressed to extrude the 0.5 cm ribbon of the gel in 10 second and the extrudability of formulations was checked [3, 8].

Drug content

A specific quantity 1g of gel was taken and dissolved in 100ml of PBS pH 7.4. The volumetric flask containing gel solution was shaken for 2hr on mechanical shaker in order to make the drug soluble completely. This solution was filtered and estimated spectrophotometrically at 230 nm [13].

In-vitro drug release

In vitro drug release studies were carried out for the gel as mentioned in the earlier section.

Preparation of Emulgel

The optimized emulsion was incorporated into the gelling agent and the final emulgel of HHCL formulation was optimized.

Table 3: Formulation of Emulgel

Ingredients (%w/w)	HEOC	HEOH	HEOX	HECC	HECH	HECX	HESC	HESH	HESX	HESX1
Drug	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6
Olive oil	6	6	6	-	-	-	-	-	-	-
Coconut oil	-	-	-	6	6	6	-	-	-	-
Sesame oil	-	-	-	-	-	-	6	6	6	6
Span 60	3.23	3.23	3.23	2.9	2.9	2.9	3.23	3.23	3.23	-
Span 80	-	-	-	-	-	-	-	-	-	2.5
Tween 20	0.76	0.76	0.76	1.1	1.1	1.1	0.76	0.76	0.76	-
Methyl paraben	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	-
Propyl paraben	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	-
Carbopol 940	1	-	-	1	-	-	1	-	-	-
HPMC K100M	-	1	-	-	1	-	-	1	-	-
Xanthan gum	-	-	2	-	-	2	-	-	2	2
Purified water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Evaluation of Emulgel

Emulgel formulations were evaluated for clarity, pH, spreadability, viscosity and extrudability.

Drug Content

500mg of emulgel was taken and dissolved in 100ml of pH 7.4 PBS. The placebo gel 500mg was dissolved in the same buffer solution. The volumetric flasks were kept for shaking for 15min. The solution was passed through the Whattmann filter paper no.42 and filtered. Appropriate dilutions were done, and the drug content was measured spectrophotometrically against corresponding placebo gel at 230nm.

In vitro diffusion study

Diffusion study of the emulgel was performed using Franz diffusion cell. The cell was locally fabricated, and volume of receptor compartment was 25ml. The dialysis membrane was mounted be Tween the donor and receptor compartments. Emulgel formulation (1g) equivalent to 36mg of drug were taken on the dialysis membrane and the compartment clamped together. The receptor compartment was filled with PBS pH 7.4 and the hydrodynamics in the receptor compartment was maintained by stirring on a magnetic stirrer at 600rpm. At pre-determined time intervals, 4ml of samples were withdrawn and an equal volume of buffer was replaced. The samples were analyzed after appropriate dilution for drug content spectrophotometrically.

Skin irritation studies

Skin irritation studies were performed on rabbits after the approval by the Institutional animal ethical committee.

A primary skin irritation test was performed since skin is the vital organ through which the drug is transported. The test was carried out on three healthy rabbits weighing between 1.5-2 kg. The test was conducted on an unbraided skin of rabbits. Before placing the formulations, the unbraided skin was cleaned with rectified spirit. The control, placebo formulation was placed on the left dorsal surface of each rabbit, whereas the standard irritant and test formulation (with drug and chemical enhancer) was placed on the right dorsal surface of the same rabbits, and the other rabbit was kept as control. The formulations were removed after 24hrs and the skin was examined for erythema/edema. The mean erythema scores were recorded depending on degree of erythema: no erythema= 0, slightly erythema (barely perceptible –light pink) = 1, moderate erythema (dark pink) = 2, moderate to severe erythema (light red) =3, and severe erythema (extreme redness) = 4.

Stability studies

The stability studies were carried out by keeping optimized formulations in glass containers with polypropylene closure for one month at room temperature. A known amount of gel was taken out at different time intervals like 0, 1st, 2nd, 4th week and analyzed for appearance, pH, drug content and viscosity [16,17].

RESULTS AND DISCUSSION

Drug-excipients compatibility study by FTIR

The spectrum of HHCL and physical mixture of HHCL with excipients (HPMC K 100 M, Carbopol, Xanthan Gum) were recorded and compared. The peaks representing the HHCL are same as in HHCL with excipients in spectrum. These results suggest that there is no interaction between HHCL and excipients used in formulation.

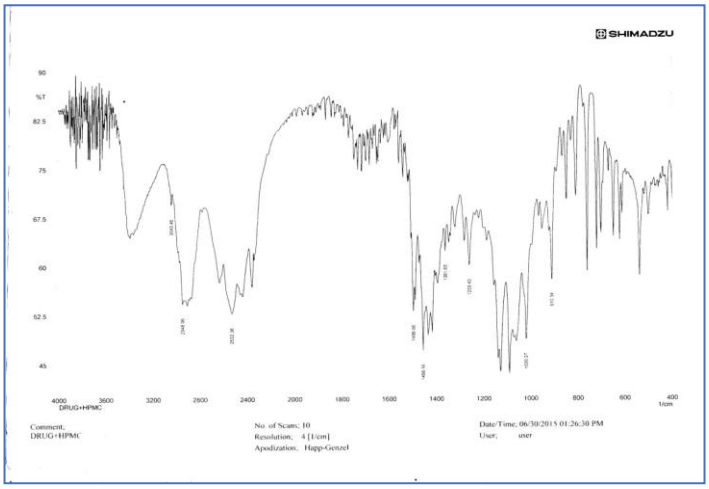

Figure 1: FTIR graph of pure drug and HPMC mixture

In vitro release of prepared emulsions

In vitro diffusion studies were performed for the optimized formulations HEO, HES, HEC.

Fig. 2 represents the *invitro* release pattern. HES formulation containing sesame oil, Tween 20, and Span 60 showed highest release. This may be due to triglycerides of singly unsaturated oleic acid and the doubly unsaturated linoleic acid, besides a small percentage of saturated fats which enables the permeating property of the sesame oil. Tween 20 is a freely soluble non-ionic surfactant which can form stable emulsion in presence of Span 60. The formulation containing Tween 20 was able to increase the drug release. An *in vitro* diffusion study was conducted for the HES1 w/o emulsion formulation and release was found to be 48.7% at the end of 8th hr. The release was less when compared to the HES formulation.

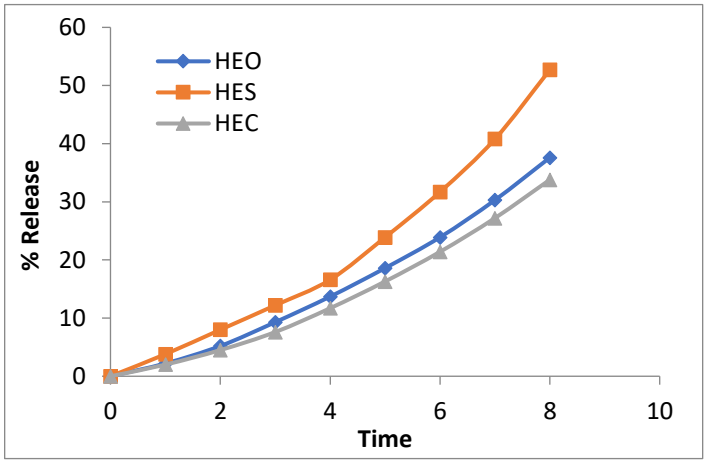

Figure 2: *In vitro* drug release profile for HEO, HES, HEC emulsion formulations

Table 4: Evaluation of optimized formulations of gels

Formulation	pH± SD	Viscosity (cps)± SD	Spreadability (g.cm/sec)± SD	Extrudability	Drug content± SD
HGC	6.9±0.05	39330±30.10	8.7±0.04	+++	95±0.5
HGH	6.5±0.06	42350±25.25	8.4±0.12	+++	92±1.1
HEX	6.1±0.09	21990±21.65	8.9±0.15	+++	98±0.5

The gel formulations were also evaluated for color, homogeneity and clarity, the results were found to be satisfactory.

In vitro release of prepared gels of HHCL

HGX formulation containing xanthan gum showed highest release.

Evaluation of optimized formulations of emulgel of HHCL

All the evaluation tests like physical appearance and homogeneity, clarity, pH determination, spreadability, extrudability, drug content and viscosity have been performed.

In vitro release studies of prepared emulgel of HHCL

An *in vitro* diffusion study was conducted for the optimized HESX1 emulgel formulation, and it showed the release of 76.7% at the end of 8th hr. HEOX, HECX, HESX was optimized based on the different oils and the highest release of 92.1, 85.5 and 95.5(%) respectively within 8 hrs. HESX formulation showed the highest release.

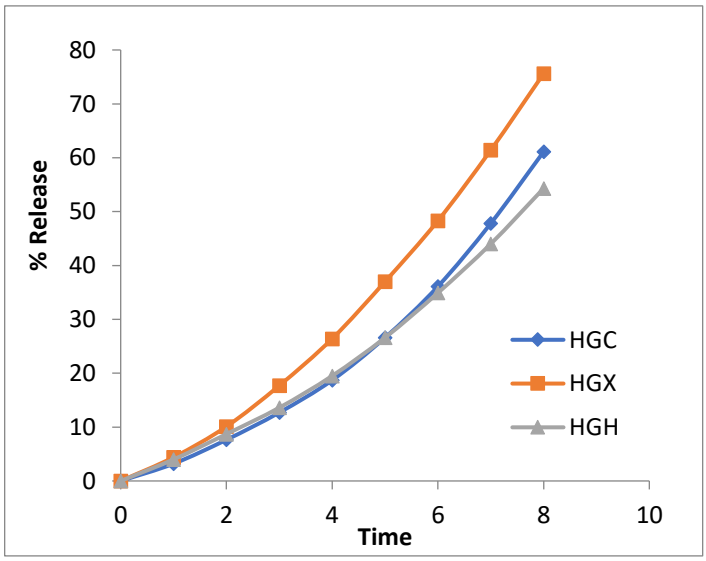

Figure 3: *In vitro* drug release profile for HGC, HGX, HGH gel formulations

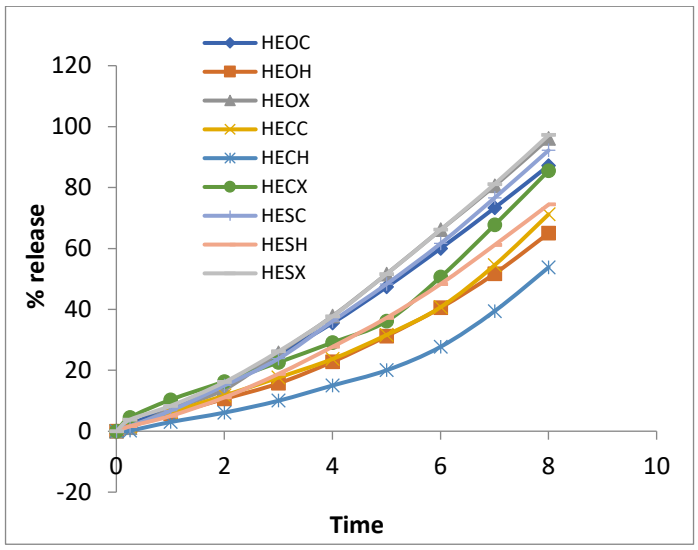

Figure 4: *In vitro* drug release profile for various (HEOC – HESX) emulgel formulations

In vitro drug release kinetics

The data was subjected to goodness of fit test by linear regression analysis according to zero order, first order kinetic equations. Higuchi's and Korsemeyer model determines the mechanism of the drug release. Release kinetics of optimized formulations was calculated from the r values. It was found that r of zero order plots were in the range of 0.91 to 0.98 whereas the r values of first order plots were in the range of 0.964 to 0.985 indicating that the drug release was first order release.

It was observed that the r values for the Higuchi's plots were found to be in the range of 0.98 to 0.99 indicating that the release of drug from these formulations was governed by diffusion-controlled process. When Korsemeyer Peppas equation was fitted to diffusion data values, the exponent 'n' was found to be in the range of 0.4 to 0.8 indicating the release mechanism followed Fickian diffusion.

Table 5: I*n vitro* drug release kinetics of optimized formulations

Formulations	r^2				Q8	n	Release mechanism	Release rate-$\mu g/cm^2/hr^{1/2}$
	zero	First	Higuchi	Peppas				
HEOC	0.981	0.985	0.941	0.973	87.2	0.8	Anomalous	184.6
HEOH	0.915	0.985	0.986	0.985	65	0.4	Fickian	201.5
HEOX	0.92	0.986	0.948	0.913	96.1	0.5	Fickian	251.8
HECC	0.943	0.964	0.931	0.936	71.2	0.7	Fickian	153.9
HECH	0.91	0.984	0.934	0.930	53.8	0.5	Fickian	207.4
HECX	0.985	0.970	0.962	0.957	85.5	0.4	Fickian	241.0
HESC	0.961	0.972	0.990	0.986	92.2	0.6	Anomalous	207.5
HESH	0.919	0.98	0.983	0.971	74.4	0.5	Fickian	239.7
HESX	0.950	0.985	0.983	0.98	97.2	0.5	Fickian	232.6

Ex vivo skin permeation studies

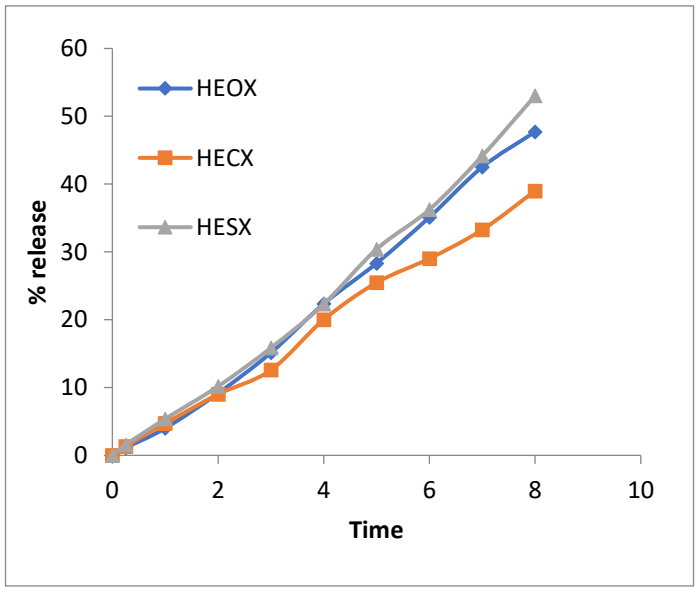

Figure 5: *Ex-vivo* drug release profile with HEOX, HECX, HESX optimized formulations

Ex vivo drug release kinetics of optimized formulations

From r^2 values it was found that drug release followed first order. The drug release from the system was diffusion limited as it obeys Higuchi model equation, from the 'n' value of Korsemeyer Peppas equation release mechanism was found to be Fickian diffusion. HESX1 formulation was prepared with combination of Span 80, sesame oil with Xanthan gum showed least *ex vivo* release of 42%.

Comparison of emulsions, gels and emulgels

The % releases of optimized formulations were compared with pure drug that showed the 35.4% release which was less when compared to the other formulations. o/w emulsion HES formulation showed 52.7% release after the 8 hrs and HES1 w/o emulsion formulation showed 48.7% after 8 hrs.

Xanthan gum formulation HGX showed the release of 75.6%. The w/o emulgel showed the highest ex *vivo* release of 53% and the optimized w/o emulgel showed 42.3%. Thus, the o/w emulgel was optimized as it showed the highest release within 8 hrs. w/o emulgel showed less permeation of drug after the 8 hrs.

Table 6: *Ex vivo* drug release kinetics of optimized formulations

Formulations	Flux (µg/cm²/hr)	Permeability coefficient (cm/hr)	Release rate µg/cm²/hr$^{1/2}$	r²				n	Type
				Zero	First	Higuchi	Peppas		
HEOX	43.94	2.44	155.8	0.945	0.995	0.996	0.984	0.5	Fickian
HECX	41.6	2.31	145.3	0.972	0.973	0.994	0.98	0.5	Fickian
HESX	44.5	2.47	154.2	0.979	0.973	0.981	0.976	0.5	Fickian

Table 7 Comparison of emulsions, gels and emulgels

Time (hrs)	Pure drug (%)±SD	*IN-VITRO*		*EX -VIVO*		
		HES (%)±SD	HES1 (%)±SD	HGX (%)±SD	HESX (%)±SD	HESX1 (%)±SD
1	2.3±1.14	3.8±0.05	2.8±0.09	4.4±0.04	5.3±0.06	3.1±0.05
2	6.81.12	8±1.12	6.2±0.05	10.1±0.05	10.1±0.05	6.8±0.06
3	10.21.10	12.2±0.02	11.2±0.06	17.7±0.05	15.8±0.04	11.5±0.04
4	15.81.12	16.6±0.05	15.6±0.05	26.4±0.04	22.3±1.1	19.9±0.04
5	19.61.10	23.9±0.06	22±0.06	37±1.02	30.4±0.02	22.8±1.01
6	21.81.10	31.7±0.05	32.6±0.02	48.3±0.08	36.2±0.05	29.7±0.08
7	27.91.15	40.8±0.08	39.8±0.05	61.4±0.04	44.1±0.04	33.8±0.09
8	35.41.12	52.7±0.04	48.7±0.06	75.6±0.06	53±0.06	42.3±0.05

Skin irritation studies

Skin irritation study was performed on rabbit. The standard irritant solution, control (drug solution), placebo formulation and formulation HESX were applied on the back of rabbit. The formulations were kept for 72 hrs and observed for any signs of skin irritation for every 24 hrs which were compared with the control rabbit which was kept as control. Very slight erythema was observed for standard irritant and no erythema and edema was observed for control (HHCL drug solution), placebo (formulation without drug) and HESX irritation score was zero.

Stability studies

The stability of this optimized formulation was known by performing stability studies for one month at room temperature on optimized formulation and the formulation was found to stable, with insignificant change in the appearance, drug content, viscosity and pH.

CONCLUSION

Emulgel of HHCL using the selected fixed oils, emulsifying agents and gelling agents were prepared. Drug (HHCL) was successfully incorporated into the emulgel of sesame oil in the concentration of 6% w/w, with Tween 20 (0.77 %), Span 60 (3.23 %) and xanthan gum (2 %) in the optimized formulation. The formulation not only exhibited satisfactory physical properties but also showed maximum drug release.

O/w type of emulgel (HESX) was optimized as it showed the release of 53% at the end of 8 hrs. W/o type of emulgel (HESX1) showed 42.3% release only after 8 hrs. Thus, it was concluded that emulgel of HHCL was a promising transdermal formulation for the treatment of localized urticaria.

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