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Research Article

Effect of Transcutol and Stearylamine on Ibuprofen Hydrophilic Gel for Transdermal Delivery

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ABSTRACT
Transdermal drug delivery system (TDDS) shows promising results when compared with oral drug delivery system mainly by eliminating the first pass metabolism and by improving the bioavailability of drug. Hydrophilic gels are networks of polymer chains that are sometimes found as colloidal gels in which water is the dispersion medium. Ibuprofen, non-steroidal anti-inflammatory drug used to relieve pain, reduces fever and anti-inflammation. The purpose of present research is to demonstrate the influence of various enhancers (transcutol and stearylamine) in various concentrations on percutaneous permeation of ibuprofen hydrophilic gel from HPMC K4M & HPMC K100M gel formulation. Gelling agents at various concentrations were preliminary screened for gel consistency. The control and the prepared gels were evaluated for clarity, homogeneity, spreadability, extrudability, drug content, *invitro* diffusion, *ex-vivo* permeation, skin irritation, anti-inflammatory activity and stability studies. All formulations have shown better physicochemical properties. Ex-vivo skin permeation studies reveals that the (IBU29) formulated using HPMC K4M 6%, transcutol 40% and stearylamine 4% as permeation enhancers has shown maximum drug release of 86.4 % for 24hrs. Permeability parameters like flux were found to be 1940.68±0.06µg/cm²/hr, permeability coefficient was found 31 $\times 10^{-3}$cm/hr and Q_{24} was found to be 5240.82±0.06µg/cm² and enhancement ratio of 13.06 over pure drug. Skin irritation studies showed irritation potential of "0" score thus providing to be non-irritant. The anti-inflammation studies were performed with inflammation induced by carrageenan 1% w/v solution. Optimized formulation (IBU29) showed highest reduction of inflammation comparable to marketed preparation BRUGESIC GEL®. The formulations were stable at room temperature for 1 month.
Key words: Transdermal gel, Ibuprofen, HPMC K4M, HPMC K100M, Penetration- enhancer.

INTRODUCTION

At present, the most common form of delivery of drugs is the oral route. While this has the notable advantage of easy administration, it also has significant drawbacks; namely poor bioavailability due to hepatic metabolism (first pass) and the tendency to produce rapid blood level spikes leading to a need for high and/or frequent dosing, which can be both cost prohibitive and inconvenient[1].

Transdermal drug delivery system is the integral part of therapeutic window for prolong period of time ensuring novel drug delivery system. It is defined as self-contained discrete dosage form which when applied transdermaly provides systemic circulation at controlled rate[2].

The success of transdermal delivery depends on the ability of the drug to permeate the skin in sufficient quantities to achieve its desired therapeutic effects. The skin is very effective as a selective penetration barrier. Percutaneous absorption involves the passage of the drug molecule from the skin surface into the stratum corneum under the influence of a concentration gradient and its subsequent diffusion through the stratum corneum and underlying epidermis through the dermis and into the blood circulation. The skin behaves as a passive barrier to the penetrating molecule. The stratum corneum provides the greatest resistance to penetration and it is the rate-limiting step in percutaneous absorption[3].

The non-steroidal anti-inflammatory drugs (NSAID's) are having excellent anti-inflammatory and analgesic activity but NSAID's produces GIT ulceration, liver and kidney trouble in case of oral administration. To avoid the adverse effect, alternate routes of administration have been tried by investigators[4].

The present work investigates the effectiveness of transcutol and stearylamine individually or in combination, as potential enhancers of ibuprofen permeation from HPMCK4M, HPMCK100M hydrophilic gels through dialysis membrane and rat skin.

Transcutol is powerful solubilising agent used in several dosage forms and seems to be very attractive as a penetration enhancer due to its non- toxicity, biocompatibility with skin and optimal solubilising properties for number of drugs. Recent studies have shown that the transcutol significantly increases the percutaneous penetration of the various active substances[5]. Stearylamine reduced the ordered intercellular lipid domains of the stratum corneum
thereby providing pathway of lower resistance for the drug transport[6].

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Table 1: Composition of Ibuprofen hydrophilic gels with permeation enhancers.

Formulation code	Ingredient (%w/w)							
	Ibuprofen	HPMC K4M	HPMC K100M	PEG 400	Propanol	Transcutol	Stearylamine	D.W up to
IBU1	6	5	–	10	30	10	–	100g
IBU2	6	5	–	10	30	20	–	100g
IBU3	6	5	–	10	30	30	–	100g
IBU4	6	5	–	10	30	40	–	100g
IBU5	6	5	–	10	30	–	2	100g
IBU6	6	5	–	10	30	–	3	100g
IBU7	6	5	–	10	30	–	4	100g
IBU8	6	6	–	10	30	10	–	100g
IBU9	6	6	–	10	30	20	–	100g
IBU10	6	6	–	10	30	30	–	100g
IBU11	6	6	–	10	30	40	–	100g
IBU12	6	6	–	10	30	–	2	100g
IBU13	6	6	–	10	30	–	3	100g
IBU14	6	6	–	10	30	–	4	100g
IBU15	6	–	5	10	30	10	–	100g
IBU16	6	–	5	10	30	20	–	100g
IBU17	6	–	5	10	30	30	–	100g
IBU18	6	–	5	10	30	40	–	100g
IBU19	6	–	5	10	30	–	2	100g
IBU20	6	–	5	10	30	–	3	100g
IBU21	6	–	5	10	30	–	4	100g
IBU22	6	–	6	10	30	10	–	100g
IBU23	6	–	6	10	30	20	–	100g
IBU24	6	–	6	10	30	30	–	100g
IBU25	6	–	6	10	30	40	–	100g
IBU26	6	–	6	10	30	–	2	100g
IBU27	6	–	6	10	30	–	3	100g
IBU28	6	–	6	10	30	–	4	100g
IBU29	6	6		10	30	40	4	100g
IBU30	6	–	6	10	30	40	4	100g

The aim of this study was to develop suitable transdermal gel formulations of ibuprofen using various gelling agent with permeation enhancers in order to reduce adverse drug reaction associated with oral formulations.

MATERIAL AND METHODS

Materials

Ibuprofen was from Medico Remedies Pvt. Ltd. Mumbai. HPMC K4M, HPMC K100M was from Yarrow chem. Ltd, Mumbai. Poly ethylene glycol 400, Propanol, Transcutol, and Stearylamine were from S.D fine chemicals, Mumbai.

Drug-excipient compatibility studies

The spectrum analysis of ibuprofen and polymer which employed in the preparation of gels was studied by Fourier Transform Infra-Red (FTIR) Spectroscopy. FTIR spectra were recorded by preparing potassium bromide (KBr) disks using a Shimadzu Corporation (Kyoto, Japan) facility (model - 8400S). Potassium bromide (KBr) disks were prepared by mixing few mg of sample with potassium bromide by compacting in a hydrostatic press under vacuum at 6-8 tons pressure. The resultant disc was mounted in a suitable holder in IR spectrophotometer and the IR spectrum was recorded from 4000 cm^{-1} to 200 cm^{-1}. The resultant spectrum was compared for any spectral changes. They were observed for the presence of characteristic peaks for the respective functional group in the compound. FTIR study was carried out to check compatibility of drug and excipients[7].

Solubility studies

Saturated solution of ibuprofen was prepared in three solvents (water, transcutol and polyethylene glycol 400). Suspension solutions were kept in an orbital shaker for 24 hours at room temperature. Later they were centrifuged for 15mins at 3000rpm, aliquots were filtered through Whatmann No. 41 filter paper. The filtrates were diluted appropriately in distilled water and assayed spectrophotometrically at 225nm[8].

Preparation of ibuprofen transdermal gel with different chemical permeation enhancers[9]

Accurately weighed required quantities of semi-synthetic polymers (HPMC K100M, HPMCK4M) at different concentration were soaked in distilled water for 2-3 hrs with continuous stirring to form a homogenous mass. Poly ethylene glycol 400 (1ml) was added slowly with stirring. Accurately weighed ibuprofen (according to Table 1) was dissolved in 3 ml of propanol then the drug solution was added slowly with stirring (300-600 rpm) in
the previously prepared polymer gel. Penetration enhancers were added with stirring either directly transcutol or after dissolved in Propanol (stearylamine).

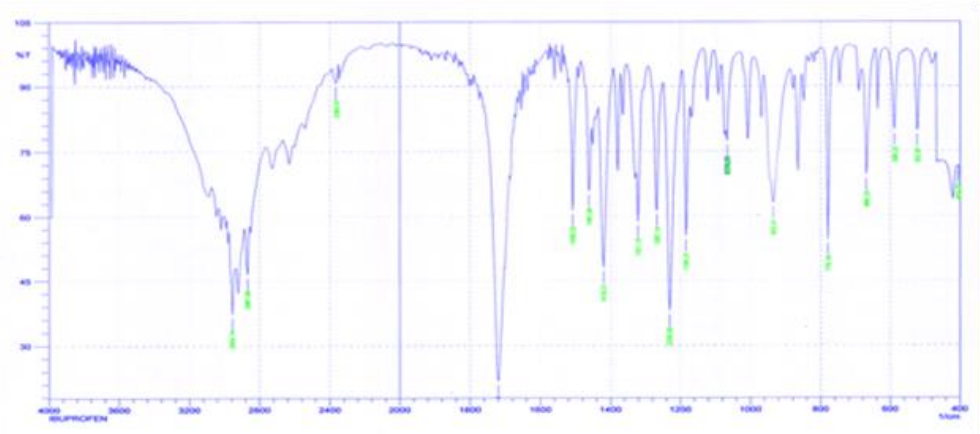

Figure 1: FTIR spectra obtained for pure drug (IBU).

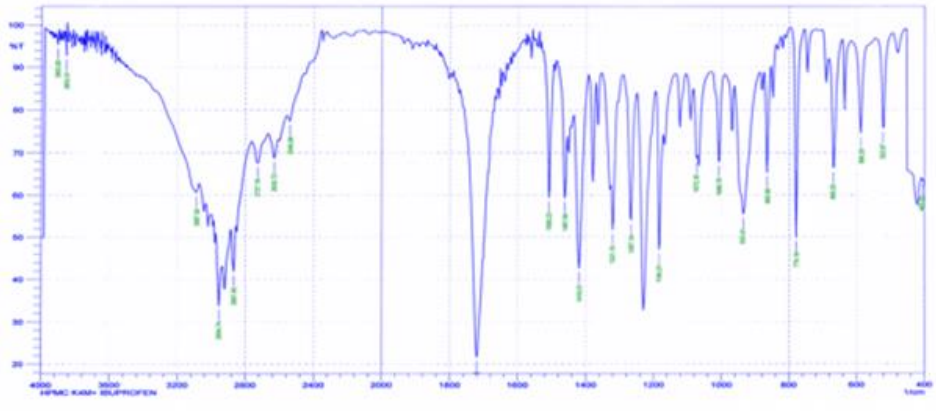

Figure 2: FTIR spectra obtained for IBU+HPMC K4M.

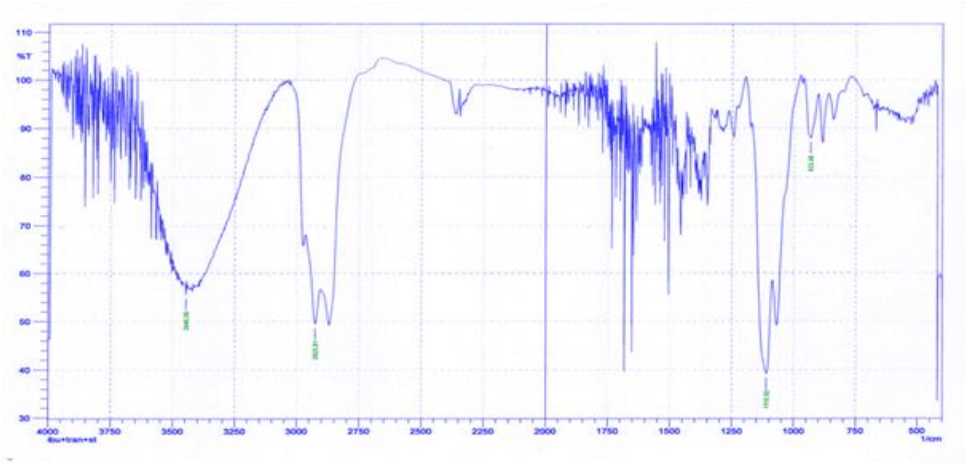

Figure 3: FTIR spectra obtained for optimized formulation IBU29

The final quantity was made up to 10 gm with distilled water[10].

Physicochemical evaluation of Transdermal gels

Determination of pH

The pH of formulation was determined by using digital pH meter by dispersing one gram of gel in 100 ml pH 7.4 phosphate buffer saline and stored for 2 hours at constant temperature. The measurement of pH for each formulation was done in triplicate and average values were calculated[8].

Drug content

500 mg of gel (equivalent to 30mg of drug) was taken and dissolved in 100 ml of pH 7.4 phosphate buffer saline. The volumetric flasks were kept for shaking for 15min. The solution was passed through Whatmann no.41 filter paper and appropriate dilutions were done and the drug content was measured against corresponding placebo gel at 225 nm[7].

Homogeneity

It was determined by visual inspection for the appearance of gel and presence of any aggregates[11].

Extrudability

Table 2: Physicochemical properties of the optimised formulations.

Formulation code	pH	Homogeneity	Spreadability (g.cm/sec)	Extrudability	Drug content%	Viscosity (Cps)
IBU4	6.44±0.35	+++	18.00±0.25	+++	95.44±0.35	38200±170
IBU7	5.58±0.26	+++	17.50±0.54	+++	97.58±0.26	39700±160
IBU11	5.77±0.23	+++	18.25±0.36	+++	97.77±0.23	39400±140
IBU14	5.77±0.38	+++	18.25±0.26	+++	98.77±0.38	39800±120
IBU18	5.94±0.17	+++	18.50±0.32	+++	98.94±0.17	38400±110
IBU21	6.34±0.48	+++	17.75±0.42	+++	96.34±0.48	42700±180
IBU25	5.62±0.34	+++	19.00±0.42	+++	97.62±0.34	39300±140
IBU28	5.74±0.13	+++	18.25±0.24	+++	98.74±0.13	36200±120
IBU29	6.68±0.12	+++	22.25±0.23	+++	99.78±0.12	38300±110
IBU30	5.83±0.15	+++	20.00±0.12	+++	98.83±0.15	40500±130

Note: Values are expressed as mean ±SD, n=3
Homogeneity : +++ very clear, ++ clear, + turbid; Extrudability: +++ Excellent, ++ good, + satisfactory

Table 3: *In-vitro* diffusion studies of optimised ibuprofen hydrophilic gel formulations through dialysis membrane.

Form.code	% drug release							Release rate (mg/cm²/hr½)
	1(hr)	2(hr)	3(hr)	4(hr)	5(hr)	6(hr)	7(hr)	
F4	4.32±0.17	5.65±0.11	6.57±0.09	7.43±0.16	8.93±0.14	9.55±0.14	10.98±0.15	0.273±0.03
F7	3.68±0.09	5.57±0.19	6.52±0.15	7.10±0.12	8.55±0.07	9.53±0.11	10.18±0.13	0.223±0.07
IBU4	9.47±0.09	12.70±0.13	15.53±0.15	18.93±0.09	20.20±0.06	30.20±0.01	43.60±0.17	1.019±0.12
IBU7	9.22± 0.09	12.03±0.04	18.35±0.19	19.45±0.02	23.27±0.01	30.73±0.15	52.73±0.03	1.513±0.01
IBU11	9.88±0.06	14.78±0.06	19.20±0.03	35.47±0.16	50.2± 0.03	66.2± 0.05	70.67±0.12	1.928±0.03
IBU14	8.30± 0.07	12.27±0.04	15.23±0.09	19.00±0.03	31.87±0.08	41.86±0.01	57.53±0.03	1.564±0.02
IBU18	14.40±0.05	19.35±0.15	32.87±0.09	40.74±0.13	58.73±0.19	60.07±0.04	73.07±0.18	1.924±0.02
IBU21	7.45±0.01	10.17±0.04	14.95±0.19	17.93±0.14	28.07±0.04	49.47±0.01	63.07±0.03	1.772±0.01
IBU25	8.15±0.15	12.88±0.04	16.03±0.05	21.00±0.06	38.33±0.18	46.93±0.02	65.67±0.17	1.826±0.03
IBU28	8.12±0.07	11.85±0.18	15.52±0.09	16.53±0.14	31.13±0.03	46.13±0.05	60.73±0.16	1.730±0.03
IBU29	10.57±0.07	15.85±0.01	18.13±0.08	37.20±0.04	51.13±0.07	66.40±0.01	76.80±0.01	2.306±0.01
IBU30	13.22±0.09	16.45±0.05	19.87±0.04	38.40±0.03	50.87±0.02	63.4±0.09	74.40±0.08	2.188±0.07

Note: Form. Code refers to formulation code

Table 4: Permeability parameters of optimized formulations.

Formulation	Q_{24} (µg/cm^2)	Flux (µg/cm^2/hr)	Permeability coefficient (cm/hr×10^{-3})	Lag time (hr)	Enhancement Ratio
Pure drug	330±0.07	14.90±0.09	2.7±0.02	3.24±0.03	1
IBU4	3628.57±0.09	144.38±0.04	23±0.02	0.86±0.06	9.689
IBU7	3351.02±0.06	136.25±0.06	22±0.04	0.81±0.02	9.144
IBU11	4865.31±0.02	172.70±0.02	24±0.03	0.62±0.03	11.590
IBU14	3869.39±0.12	160.31±0.12	26±0.11	0.69±0.12	10.759
IBU18	4685.71±0.05	165.57±0.03	27±0.08	0.58±0.09	11.112
IBU21	4044.90±0.02	151.69±0.09	24±0.02	0.73±0.13	10.180
IBU25	3951.00±0.07	148.15±0.13	23±0.13	0.67±0.06	9.942
IBU28	3657.14±0.02	141.50±0.02	27±0.01	0.76±0.09	9.496
IBU29	5240.82±0.06	194.68±0.06	31 ±0.15	0.46±0.03	13.065
IBU30	4963.27±0.04	187.16±0.15	30±0.03	0.51±0.05	12.561

Note: Values are expressed as mean ±SD, n=3

The extrudability test was carried out by Pfizer hardness tester. A 15 gm of gel was filled in aluminium tube. The plunger was adjusted to hold the tube properly. The pressure of 1kg/cm² was applied for 30 sec. The quantity of gel extruded was weighed. The procedure was repeated at three equidistance places of tube. Test was carried in triplicate[12].

Spreadability

The spreadability of the formulated gel was determined by measuring the spreading diameter of 1g of gel between 20x20 cm glass plates after 1 min. The mass of the upper plate was standardized at 150 g. The spreadability was calculated by using the formula[13].

$$S = \frac{ml}{t}$$

Where,

Table 5: Anti-inflammation studies on rats.

Animal group with six rats in each	Animal wt (gms)	Volume of left hind paw (ml)		
		0(hr)	1(hr)	2(hrs)
Control	181±6.36	1.75±0.354	1.75±0.354	1.75±0.354
Inflamed with carrageenan 1% (w/v)	218.5±4.23	2.95±0.041	3.2±0.034	3.5±0.091
Inflamed + marketed gel	176± 5.85	2.7±0.051	2.1±0.021	1.9±0.283
Inflamed + IBU29	192±4.65	2.8±0.037	1.95±0.032	1.8±0.06

Note: Values are expressed as Mean ±SD

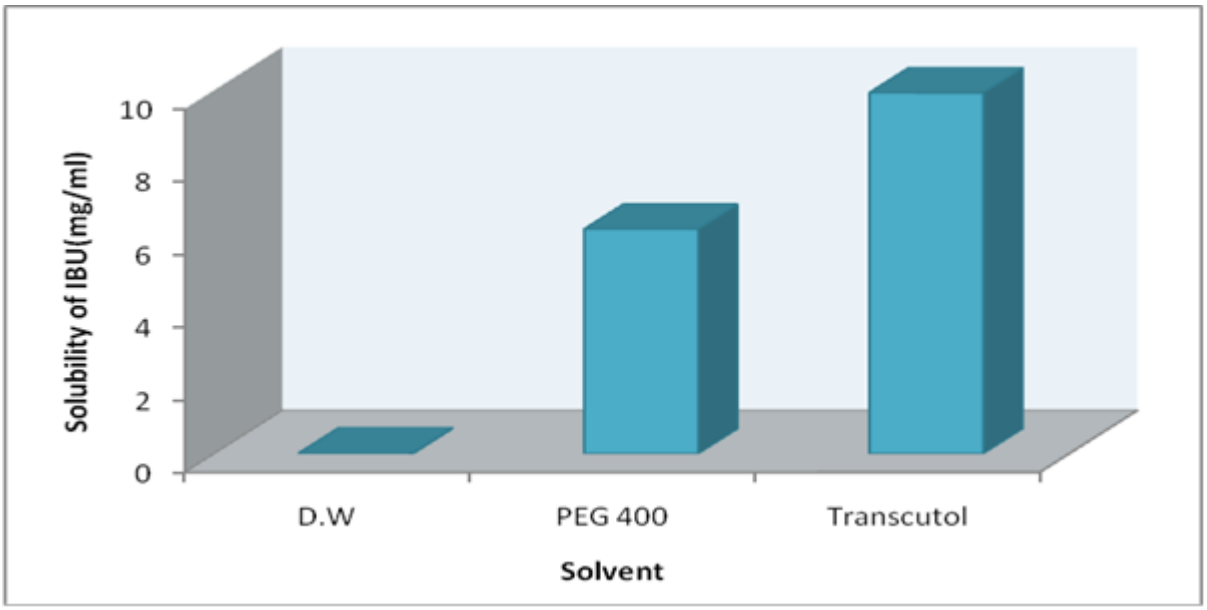

Figure 4: Solubility of IBU in different solvents.

S = spreadability
m = weight tied to the upper glass slide
l = length of the glass slide
t = time taken in seconds

Determination of viscosity

Viscosity of prepared gels was determined by Brookfield programmable viscometer LV DV-II PRO. The spindle number 64 was rotated at 10rpm. Samples of the gels were allowed to settle over 30 minutes at room temperature before taking the measurements. The determination of viscosity for each formulation was done in triplicate and average values were calculated[14].

In-vitro diffusion studies

Diffusion studies were performed using Franz diffusion cell. The cell was locally fabricated and the volume of receptor compartment was 25 ml. The dialysis membrane used for diffusion studies was placed between donor and receptor compartment. 500 mg of gel formulation was uniformly applied on membrane and clamped together.

The receptor compartment was filled with pH 7.4 phosphate buffer saline and maintained by continuous stirring with a magnetic bead at 600 rpm. At predetermined time intervals, 1ml samples were withdrawn and replaced with equal volume of buffer. The samples were analyzed after dilution using spectrophotometer[15].

Release rate

It was calculated from the plot of amount of drug permeated versus square root of time. The slope is release rate (µg/cm²/hr^{½}).

Ex-vivo permeation studies

The experimental protocol was approved by the institutional animal ethical committee (IAEC) (ID number: GPRCP/IAEC/20/16/02/ PCE/ACE-7). Male wistar rats (150-180g) were used for permeation study. The animal was sacrificed by cervical dislocation and hair was removed from abdomen using an animal hair clipper. Abdominal skin section was excised and observed for existence of cuts and wounds. The fat adhering on dermis was removed using scalpel and finally it was washed under tap water. The skin was stored at −20°C and used within a week[9]. For the permeation studies locally fabricated Franz diffusion cells with 25 ml receptor volume were used. The thawed rat skin was mounted onto diffusion cell such that the dermis side was in constant contact with receptor solution. 500 mg of gel was applied to the stratum conium facing the donor compartment and the hydrodynamics in the receptor compartment were maintained by stirring on magnetic stirrer at 600 rpm. 1 ml sample was withdrawn at predetermined time intervals for 24 hours and drug content was analyzed by UV-VIS double beam spectrophotometer at 225 nm.

Calculation of permeability parameters

Steady state flux (µg/cm²/hr)

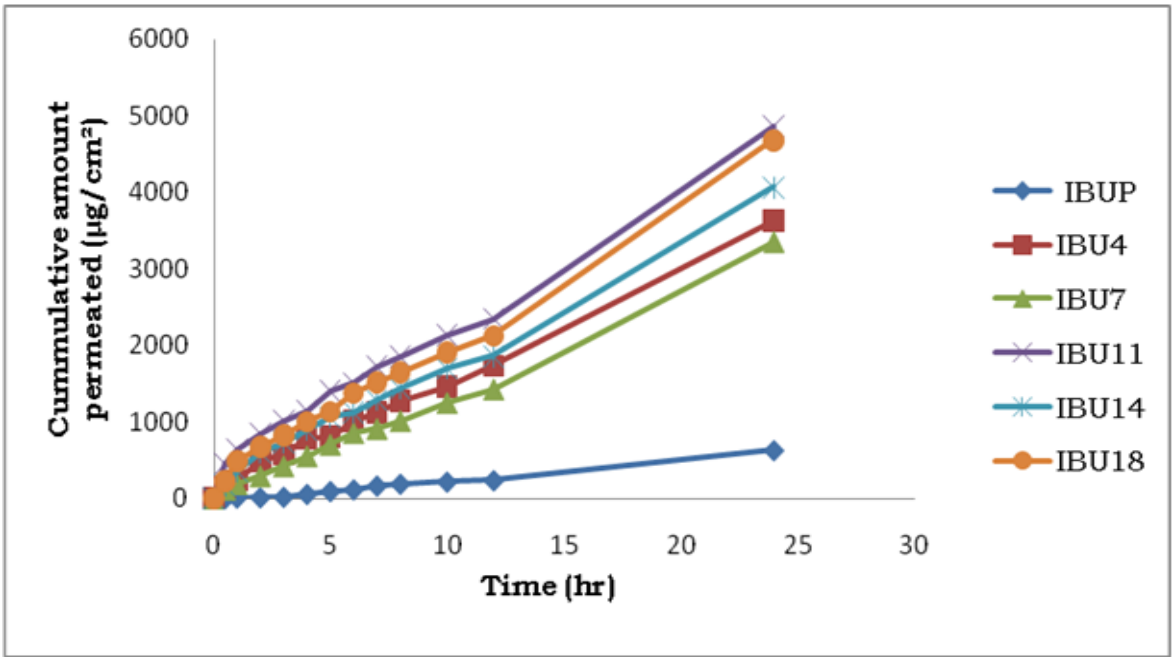

Figure 5: *ex-vivo* permeation profile of optimised formulations -1 .

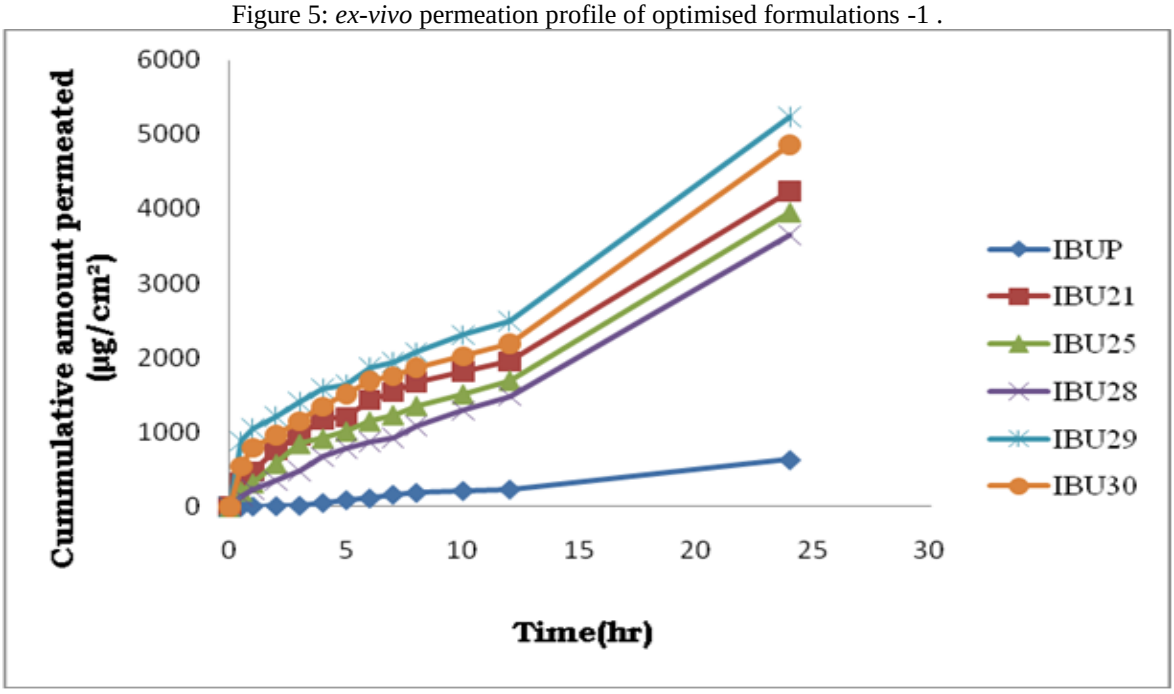

Figure 6: *ex-vivo* permeation profile of optimised formulations -2.

Steady state flux **(**Jss) is defined as the rate of diffusion or transport of a substance through a permeable membrane. After reaching the steady state of drug permeation, flux was calculated using the following equation[17].

$$Jss = \frac{dM}{S}.dt$$

dM - amount of drug permeated
S - unit cross-section area
t - time (t).

The steady state flux obtained by plotting the cumulative amount of drug permeated in micrograms per square centimetre versus time in hours and the slope is the flux. Lag time is X intercept of this graph.

Permeability coefficient (cm/hr)

The permeability coefficient (Kp) was calculated with the following equation[17].

$$\mathbf{Kp} = \frac{\mathbf{Jss}}{\mathbf{CV}} \square$$

Where,
cv is the total donor concentration of the formulation.

Enhancement ratio

Enhancement ratio (ER) used to evaluate the effect of permeation enhancer on diffusion and permeation of selected drug molecules and is calculated by[17]

$$\mathbf{ER} = \frac{\mathbf{Jss}\text{ of drug with enhancer}}{\mathbf{Jss}\text{ of drug alone}}$$

Where,
Jss - Steady state flux

Drug kinetics

Regression coefficient (r^2) was calculated for all the formulations. Release component "n" was calculated from Korsemeyer-peppas equation. These calculations were carried out using MS-office excel.

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 two 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. On the first rabbit, the right dorsal surface was kept as control, whereas transcutol 40% / stearyl amine was applied on the left dorsal surface of the same rabbit. On the second rabbit, the optimized formulation (containing drug and permeation enhancer) was applied on the right dorsal surface, whereas placebo gel was applied left dorsal surface of the same rabbit. The experiment was carried out for 3 days and the application sites were graded according to the Draize method[18].

Anti-inflammation studies

Anti-inflammation studies were performed on rats, using carrageenan solution for inducing inflammation. Animal studies were approved by Institutional animal ethical committee. Rats were divided into four groups with six animals in each; Group-1: un-inflamed, injected with saline; Group-2: inflamed, injected with carrageenan %1 solution; Group-3: inflamed, treated with the reference product (BRUGESIC GEL®); Group-4: inflamed, treated with the test ibuprofen optimized formulation**.** The animals were placed singly in observation chambers for 10 min to minimize any stress-related behavioural changes. The rats then received sub-plantar administration of 50 µl of the carrageenan (1% w/v, in normal saline) in the left hind paw and were returned immediately to the observation chamber. The volume (ml) of the paw was measured at 0, 1, 2, 3 and 4 h after
carrageenan administration. The gel formulations or the reference were applied to the plantar surface of the left hind paw by gently rubbing 0.5 g of the formulation 50 times with the index finger and compare with control using plethysmograph instrument[19].

Stability studies

Stability studies were carried out by keeping optimized formulations in glass containers with polypropylene closure for one month at room temperature. Known amount of gel was taken out at different time intervals like 0, 1st, 2nd, 4th week and was analyzed for appearance, pH, drug content and viscosity[8].

RESULTS AND DISCUSSIONS

Drug Excipients compatibility studies

Ibuprofen compatibility with excipients was studied by FTIR. From FTIR spectrums of the pure drug figure 1 and those of blend with polymer figure 2 and optimized formulation figure 3 , the peaks identified in the pure drug ($1720cm^{-1}$, $2953.45\ cm^{-1}$, $2360.44\ cm^{-1}$, $1227.47\ cm^{-1}$) were relatively same when compared with the blend and optimized formulation, hence indicating no drug excipients interaction i.e. the pure drug was not altered functionally and compatible with excipients.

Solubility studies

Maximum solubility of ibuprofen was shown by transcutol (9.94±0.87mg/ml) followed by poly ethylene glycol 400 (6.19±0.65mg/ml) when compared with water (0.029±0.86mg/ml) (shown in Figure 4). The transcutol is known as powerful solubilising agent and an attractive penetration enhancer due to nontoxic, miscibility with polar and non-polar solvents and biocompatibility with the skin, so it showed maximum solubility and maximum permeation enhancer. Polyethylene glycol 400 was used in further study in preparation of ibuprofen hydrophilic gel as emollient and gelling agent, in addition it was a water miscible solvent (co-solvent) which increased the water solubility of drug[20].

Physicochemical evaluation for hydrophilic gels

All the prepared ibuprofen hydrophilic gels with permeation enhancers (transcutol and stearylamine) were evaluated for their physicochemical properties such as pH, homogeneity, spreadability, extrudability, drug content and viscosity. The pH was found to be in the range from 5.22 to 6.87, indicating suitability for application on skin. All the prepared formulation gels showed good homogeneity with absence of lumps. The developed preparations were much clear and transparent[21]. The value of spreadability varies from 10.5-22.25 g.cm/sec indicating that the gels are easily spreadable by a small amount of shear. All gel preparations indicated a good spreadability. The extrusion of the gel from the tube is important during its application and in the patient acceptance. The extrudability of all formulations was found to be good and compatible. The content of drug per 500mg of gel ranged from (95.36% to 99.78%) which indicates that efficient loading and uniform distribution of drug in the formulation.

Viscosity is an important parameter for characterizing the gels as it affects the extrudability and release of drug.

Viscosity of prepared gels was determined by Brookfield programmable viscometer LVDV-II+PRO. The spindle number 64 was rotated at 20 rpm. Samples of the gels were allowed to settle over 30 minutes at the temperature (25±1°C) and the rheological behaviour of all formulated gels systems was studied. In gel system, consistency depends on the ratio of solid fraction, which produces the structure to liquid fraction. The values of viscosity range from 32400-43200 Cps. Formulations which have shown 50% release in dialysis membrane have been optimised. Physicochemical properties results of the optimised formulations are given in Table 2.

In-vitro diffusion studies for transdermal gels

From the *invitro* diffusion studies, the formulations IBU11, IBU29 and IBU30 were shown more than 70% of drug release. The formulations IBU4, IBU21, IBU25 and IBU28 were shown more than 60% of drug release. The

Table 6: Stability studies of IBU29.

Parameters	Time in weeks for IBU29			
	O (Initial)	1st week	2nd week	4th week
Appearance	+++	+++	+++	+++
Drug content (%)	99.24±1.43	99.18±1.74	99.08±1.23	98.98±1.22
Spreadability (g.cm/sec)	25.30±0.1	23.90±0.4	26.30±0.2	24.10±0.7
pH	6.23±0.24	6.08±1.23	6.06±1.24	5.94±1.23
Viscosity(Cps)	38300±110	38300±140	38300±180	38300±120

Note: Values are expressed as mean ±SD, n=6

formations IBU7 and IBU14 were shown more than 52% of drug release for 7 hours when compared with controls due to presence of permeation enhancers (transcutol and stearylamine) which, as shown in table 3. As the in-vitro diffusion studies were performed on dialysis membrane where it contains only water filled pores but does not mimic the surface of skin, which is highly lipophilic made of phospholipids. Hence, the above formulations were studied for ex-vivo permeation on rat abdominal skin; the results might not be similar because the ibuprofen hydrophilic gel formulations contained permeation enhancers which show effect on the surface of lipophilic skin by interacting with skin or by rupturing skin integrity which does not show on dialysis membrane. So, for getting better results and to study the effect of permeation enhancers on the skin, the mentioned formulations were subjected to ex-vivo permeation studies[22].

Ex-vivo permeation studies of ibuprofen hydrophilic gel

Ex-vivo permeation studies of formulations IBUP (pure drug solution), IBU4, IBU7, IBU11, IBU14, IBU18, IBU21, IBU25, IBU28; IBU29 & IBU30 were performed with rat abdominal skin using Franz diffusion cells. Samples were withdrawn periodically and analyzed using UV-VIS double beam spectrophotometer at 225 nm. Permeation profiles are shown in Figure 5& Figure 6.

Permeability parameters of optimized formulation

The permeability parameters, cumulative amount permeated in 24hrs (Q_{24}), flux, permeability co-efficient, lag time and enhancement ratio were calculated. The formulation IBU29 has shown the maximum flux 13.068±0.06 µg/cm2/hr, permeability coefficient 31 ±0.15 cm/hr×10-3, lag time 0.46±0.03 hr, enhancement ratio 13.065, Q_{24} 5240.82±0.06µg/cm² as it contained combination of permeation enhancers (transcutol and stearylamine). Transcutol is known as powerful solubilising agent and an attractive penetration enhancer due to nontoxic, miscibility with polar and non-polar solvents and biocompatibility with the skin, so it showed maximum solubility and maximum permeation enhancer. Stearylamine reduced the ordered intercellular lipid domains of the stratum corneum thereby providing pathway of lower resistance for the drug transport[6].

Model dependent release kinetics of optimized formulations

The results obtained were attempted to fit into various mathematical models. The regression coefficient (r^2) values of zero order, first order, Higuchi, Peppas for the optimized formulations. When compared regression coefficient "r^2" values of zero order and first order plots of optimized formulation IBU29, It was shown that "r^2" value of zero order was 0.9971 whereas the "r^2" value of first order 0.9079 indicating that the drug release from optimized formulation was found to follow zero order kinetics. The "r^2" value of Higuchi was found to be 0.9842. The ex-vivo studies data as log % drug release versus log time were fitted to korsemeyer peppas equation, value of the exponent "n" was found to be 0.6170 indicating the drug release by anomalous transport.

Skin irritation study

Skin irritation study was performed by using control, transcutol 40%, stearyl amine, placebo and optimized formulation IBU29 which were applied on the left and right dorsal surface of rabbit skin and examined for three days. Erythema and edema were evaluated and the score was zero which indicated its safety and acceptability for transdermal delivery.

Anti-inflammation studies

The results obtained from the table 5, show a favourable decreasing of the left hind paw volume of rat after using optimized formulation IBU29 when compared with the paw volume of the control & marketed product (BRUGESIC Gel®). The optimized formulation contained both permeation enhancers (transcutol and stearylamine) which enhance the permeation of the gel formulation through stratum corneum and lower the resistance of the drug transport. Hence, increasing the flux, permeability coefficient and finally increasing the therapeutic effectiveness of the gel formulation in minimum time.

Stability studies

The stability of the optimized formulation was known by performing stability studies for one month at room temperature with ambient humidity. The formulation IBU29 was found to be stable with insignificant change in the appearance, drug content, pH and viscosity.

CONCLUSION

Ibuprofen hydrophilic gels of Ibuprofen were prepared and optimized. All the physicochemical properties of it were checked and were found to be acceptable. The gelling agents HPMC K4M and HPMC K100M were used in concentration (5-6%w/w). Using Permeation enhancers transcutol and stearylamine in concentration (10-40%w/w) and (2- 4%w/w) respectively. *In vitro* release of the tests formulations were performed to determine drug release rate from Ibuprofen hydrophilic gel. It was concluded that IBU4, IBU7, IBU11, IBU14, IBU18,

IBU21, IBU25, IBU28, IBU29 and IBU30 have shown more than (52%- 76%) drug release for 7 hrs respectively. *Ex-vivo* studies indicated that the IBU29 formulated with HPMCK4M in the concentration of 6 % w/w and (40%Transcutol w/w , 4% w/w stearylamine) as penetration enhancers has shown better release of ibuprofen for 24 hrs with the flux of 194.68 µg/cm^2/hr, Q_{24} 5240.82(µg/cm²) and Permeability coefficient of 31×10^{-3} (cm/ hr) . Skin irritation studies proved that the IBU29 formulation was non-irritant. Anti-Inflammatory studies proved that the IBU29 formulation decreased the Inflammation induced carrageenan 1% (w/v) solution. The IBU29 formulation was found to be stable for one month at room temperature. Hence Ibuprofen gel comparable to marketed preparation BRUGESIC GEL® was successfully formulated using transcutol and stearylamine as enhancers.

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