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Research Article

FORMULATION AND EVALUATION OF IBUPROFEN TOPICAL GEL: A NOVEL APPROACH FOR PENETRATION ENHANCEMENT

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ABSTRACT

This study aimed to increase the therapeutic effectiveness of ibuprofen by increasing its transdermal permeation, via solid dispersion incorporated in gel. 2- hydroxy propyl beta cyclodextrins (2-HPβ-CD) and β-cyclodextrin (β-CD) were used as carriers and carbopol 941 was the gelling agent. Eight solid dispersion formulations of ibuprofen were prepared using different drug: polymer ratios viz. 1:0.5, 1:1, 1:2, and 1:3 for 2-HPβ-CD and β cyclodextrin using the co-evaporation method, and were evaluated for partition coefficient, dissolution studies, and Fourier Transform Infra Red (FTIR) spectrophotometer. The optimized solid dispersion of ibuprofen was incorporated into gel and was compared with penetration enhancers. The formulations were analyzed to determine their pH, spreadability, viscosity, and *in vitro* drug release. The absence of extraneous interactions among ingredients was confirmed by FTIR, and differential scanning calorimetry (DSC). The formulation with 1:0.5 SDIB (drug: HPβCD) with a partition coefficient of 1.28 was incorporated in carbopol gel, and produced 98.21% drug release compared to solid dispersion of ibuprofen with menthol ($SDIB_{M5\%}$), which produced 96.5% drug release. In *ex vivo* studies, SDIB and $SDIB_{M5\%}$ formulations gave 94.3% and 92.36% drug release within 24h. The percent inhibitions of the edema formation by the gels were in the range of 18.32% to 67.96%, and the maximum inhibition was shown by the SDIB formulation. Therefore, SDIB formulation incorporated in gel produced better results than other formulations prepared with permeation enhancers. Stability studies conducted for SDIB incorporated gel according to International Conference on Harmonization guidelines showed it to be stable for two months.

Keywords: Ibuprofen, Topical gel, Solid Dispersion, Partition Coefficient, Penetration, Anti inflammatory activity.

INTRODUCTION

Ibuprofen[2-(4-isobutylphenyl)propionic acid], a potent non-steroidal anti-inflammatory (NSAID) drug that is often used for the treatment of acute and chronic arthritic conditions, has pH dependent solubility and permeability.[1] Although ibuprofen is highly permeable through the stomach, its poor water solubility (log P value 3.6) limits its entry into systemic circulation before gastric emptying (30 min to 2 hr) occurs.[2] During gastric empting, ibuprofen enters the small intestine, where it cannot permeate through the membrane despite being solubilised.[3] Since dissolution is the rate-limiting step during drug absorption, the poor water solubility in oral forms of ibuprofen results in low bioavailability due to erratic or incomplete absorption from the gastrointestinal tract.[4,5] Oral formulations with rapid absorption rates aid pain relief and enhance IB's analgesic properties.[6] In addition to absorption difficulties, oral formulations of ibuprofen can cause gastric mucosal damage, which may result in ulceration and bleeding.[7]

Therefore, there is a need to develop topical dosage forms of ibuprofen to minimize the gastrointestinal side-effects of oral ibuprofen, and to provide relatively consistent drug levels at the application site for prolonged periods.[8] Transdermal and topical deliveries also provide an increased bioavailability by avoiding first-pass metabolism by the liver and a consistent delivery for an extended period.[8,9] Topical delivery vehicles (creams, gels) and transdermal delivery agents (dermal patches) can improve patient compliance due to decrease in the dosage frequency. However, ibuprofen's poor permeability through human skin makes transdermal delivery difficult.[9,10,11] The stratum corneum, the external layer of the epidermis characterized by a lipid-rich rich lamellae, serves as a formidable permeability barrier for trandermal absorption of ibuprofen.[12] The permeability problems at the skin surface may be obviated by the use of drug carriers, and penetration enhancers.

Although studies have explored the potential of oral formulations like inclusion complexes, prodrug, solid dispersion method, and microcapsule, there have been few attempts to enhance the bioavailability through topical and absorption, which could be an effective way to improve ibuprofen's solubility.[13-17] The solid dispersion (SD) system, where drugs exist amorphously in polymeric carriers, has also been used to enhance dissolution and bio availability of hydrophobic drugs.[18] Studies have also shown the SD method aids dissolution of a poorly-soluble drug (aqueous solubility less than 0.1 mg/ml at 37°C) by enhancing the surface area, and reducing particle size.[19,20]

There has been limited exploration of the efficacy of the SD method to create topical formulations of ibuprofen, as the method has mainly been used to create oral formulations. This study aims to apply the SD method using 2- hydroxy propyl beta cyclodextrins (2-HPβ-CD) and β-cyclodextrins (β-CDs) as carriers. The CDs, a family of cyclic oligosaccharides, form hydrophilic inclusion complexes with functional groups on lipophilic compounds in aqueous solution. The resulting complex masks the drug's hydrophobic sites within the inner cavity of the inclusion body, while the hydrophilic functional groups are exposed to the aqueous environment.[21] Therefore, cyclodextrin based drug delivery enhances aqueous solubility and bioavailability of a lipophilic drug without changing its intrinsic ability to permeate lipophilic membranes. In addition to being a potent solubilizer, 2- HPβ-CD has been shown to potentially enhance absorption during topically applied delivery by increasing the availability of dissolved drug molecules adjacent to the biological membrane surface, or by direct action on the stratum corneum.[22]

The percutaneous absorption of drugs involves two consecutive processes: the release of the drug from the topical formulation, and its absorption into the skin at the site of application.[23] Increasing the release rate of the drug from the dosage form might therefore improve percutaneous absorption. The release rates of drugs from topical preparations depend directly on the physiochemical properties of the carrier and the drug employed. [24,25,26]

The present study will aim to study both the release rate, and the absorption properties of topically administered ibuprofen with a novel approach using solid dispersion incorporated gels with 2-HPβ-CD and β-cyclodextrin as carriers, in the presence and absence of permeability enhancers. Gel bases with various penetration enhancers were used to increase IB's dermal permeability and flux across the skin epithelia. In addition to investigating the dissolution behaviour of the topical IB, we sought to determine the diffusion

properties of IB in semisolid vehicles since diffusion is the rate-limiting step during drug release at the site of application. Finally, we determined IB's permeation through skin as well as its anti-inflammatory activity to assess the efficacy of the topical formulation. The low bioavailability of oral and systemic forms of IB coupled with the side effects necessitates the need to explore topical administration.

MATERIALS AND METHODS

Chemicals Required

Ibuprofen (gift sample from Natco Pharma Ltd), β cyclodextrin (Hi Media Laboratories Ppvt Ltd, Mumbai), 2-Hydroxy propyl β cyclodextrin (Chemika Biochemical reagents), Carbopol 941(Corel Pharma Chem., Ahmadabad), Phospholipon 80H (gifted from Lipoid Gmbph Frigenstr 4, Germany), isopropyl myristate (S.D Fine Chemicals Ltd, Mumbai),menthol (S.D Fine Chemicals Ltd, Mumbai), sodium chloride (S.D Fine Chemicals Ltd, Mumbai), propane 1-2 diol purified (S.D Fine Chemicals Ltd, Mumbai), triethanolamine LR (S.D Fine Chemicals Ltd, Mumbai).

Preparing Ibuprofen Solid Dispersion

Initial compatibility studies between ibuprofen (IB) and carriers were carried out using Fourier Transform Infra Red (FTIR) spectrophotometer, and compatible excipients were used for final formulations. 1% ibuprofen was used for the study. A physical mixture of IB was prepared by using β cyclodextrin & 2-HPBCD carriers in 1:0.5, 1:1, 1:2, 1:3, 1:4 ratios. Solid Dispersions (SDs) of IB were prepared using the solvent evaporation, and co-evaporation methods. SD through solvent evaporation was prepared by dissolving the drug and carrier in methanol with 15 minutes of stirring, and then placed in desiccators for 4 days. The resultant solid dispersion was passed through a #120 sieve. SD through co-evaporation was prepared by dissolving the drug in methanol, and the carrier in aqueous media. Subsequently, the organic drug solution was slowly added to the aqueous carrier solution followed by stirring at 300 rpm, using a magnetic stirrer at 37^0C for 24 hrs. The resultant solid dispersion was passed through a #120 sieve. The obtained products were then evaluated for polymorphic transitions by DSC.

Preparing gel formulations

Table 1 illustrates the formulae used to prepare the IB gel formulations. The formulations were prepared by soaking carbopol 941 in water for 24 hrs. The solid dispersion containing 1% drug was dissolved in ethanol and this solution was added to the above gel with continuous stirring Triethanolamine was also added subsequently. The prepared formulations were filled in lacquered aluminium collapsible tubes and stored in cool place.[27]

Assay of gel formulations

500 mg of gel (equivalent to 5mg of drug) was dissolved in 100 ml of phosphate buffer (pH 7.4) 500 mg of the placebo gel was also dissolved in the same buffer solution. The volumetric flasks were kept for shaking for 15 min. Subsequently, the solution was filtered using the Whatmann filter paper no.42. Appropriate dilutions were done and the drug content was measured spectrophotometrically against corresponding placebo gel at 222 nm.[28]

Analysis of drug release and dissolution

Dissolution studies of solid dispersion of ibuprofen (SDIB) were carried out using USP-I basket apparatus at 100 rpm for 1 hr using the 7.4 pH phosphate buffer media. The concentration of drug release was analysed using UV spectrophotometer at 222 nm.

In vitro diffusion studies

The diffusion studies were performed using a Keshary-chien diffusion cell. The cell was locally fabricated and had a 25 ml receptor compartment. The dialysis membrane was mounted between the donor and receptor compartments. The gel formulation was applied uniformly on the dialysis membrane and the compartments were clamped together. The receptor compartment was filled with the phosphate buffer (pH 7.4) and the hydrodynamics in the receptor compartment were maintained by stirring with a magnetic bead. 1ml of samples was withdrawn from the receptor compartment at pre-determined time intervals and an equal volume of buffer was replaced. The samples were analyzed after appropriate dilution for drug content spectrophotometrically at 222 nm.[29]

In vitro skin permeation

The rat epidermis was obtained from inbred adult male Wistar rats, which weighed between 130-150 gms, and were maintained under standard laboratory conditions (25 ± 1°C and 55 ± 5% relative humidity with a 12-hour light/dark cycle). The epidermis was mounted onto Keshary-chien diffusion cell in such a way that the dermis side was in constant contact with receptor solution. The receptor compartment was filled with phosphate buffer (pH 7.4). The stratum corneum was facing the donor compartment which contained the gel formulation, and the hydrodynamics in the receptor compartment were maintained by stirring with a magnetic bead. 1 ml of sample was withdrawn at pre-determined time intervals (every one hour) from the receptor compartment and an equal volume of buffer was replaced. The samples were analyzed after appropriate dilution for drug content spectrophotometrically at 222 nm. [30, 31] Menthol, phospholipon 80H, and isopropyl myristate were used as permeation enhancers. The rate of skin permeation by the drug was measured as the flux, which was calculated from the slope of the linear part of each permeation profile.

Evaluation of anti-inflammatory activity

The anti-inflammatory activity of SDIB was evaluated using the fifty-four male Wistar rats, described above. The rats were divided into nine groups with six rats in each group. The first three groups served as controls and the remaining as optimized samples containing 1% of IB or SDIB.[25]

Experimental animals

Inbred adult male Wistar rats, weighing between 130-150 g were maintained in standard laboratory conditions of laboratory conditions, at 25 ± 1°C and 55 ± 5% relative humidity with a 12-hour light/dark cycle.[32] These rats are randomly divided into 9 groups, with six in each group.

Measurement of Inflammatory Response

The first three groups served as controls, as described below:

Group - I: un-inflamed, injected with saline;

Group - II: control: inflamed, injected with carrageenan;

Group - III: standard: inflamed, treated with the reference product.

The other six groups were inflamed and treated with the following test IB formulations IB, SDIB, $SDIBIPM_{5\%}$ (SDIB incorporated in gel 5% isopropyl myristate), $SDIBM_{5\%}$ (SDIB incorporated in gel with menthol 5%), $IBPL80H_{2\%}$ (SDIB incorporated in gel 2% phospholipon 80H) and blank. Carrageenan solution (1 %w/v, in normal saline) was used to induce inflammation.

Each rat was placed in an observation chamber for 10 min to minimize stress-related behaviors. 0.5 g of the gel formulations or the reference were gently rubbed onto the plantar surface of the left hind paw 50 times with the index finger. Thirty minutes later, pleurisy was induced by injecting 50 µl of 1% w/v carrageenan solution subcutaneously into the sub-plantar surface of the left paw of the mice. Control un-inflamed animals received 50 µl of normal saline subcutaneously, into the sub-plantar surface of the left paw**.** All rats were subsequently returned to the observation chamber. The inflammatory response was assessed by measuring the volume of the paw at 0, 1, 2, and 3 h after carrageenan administration, using a plethysmometer. The percentage of inhibition of edema was recorded.

RESULTS AND DISCUSSION

In this study, we used a novel technique to design a topical formulation of ibuprofen using the solid dispersion method. Since several studies have shown that an excess of CD carriers packaged

with lipophilic drug reduces permeability through the stratum corneum, the SDIB was optimized to achieve maximum aqueous drug solubility with the least amount of carriers.[32,33] IB, SDIBs with optimized carriers, were subjected to FTIR to determine any possible interactions of the drug with the carrier. The above precaution was taken to ensure that the CD carrier was therapeutically inert, and wouldn't interfere with IB's mechanism of action. There were no significant changes in IR spectra of SDIBs when compared to the pure drug of IB (Fig 1). The DSC scan of IB showed a sharp melting endotherm at 70° C (Fig.1), which can be attributed to its melting temperature. The DSC of HPβCD showed one sharp endothermic peak at 96°C, which belongs to the HPβCD carrier. The DSC of the optimized formulation had two distinct peaks at 70°C and 96°C. Since there was no change in the temperature of the optimized formulation when compared to that of the pure forms of the drug and the carrier, there was no interaction between the drug and the excipients.

We also found that the percentage drug released by solid dispersion of IB with HPβ-CD (1:3) was higher when compared to the formulations containing pure drug and SDIB with β-CD (Table 2, Fig 2). Table 6 and Figure 5 show that SDIB, SDIBM5%, and SDIBPL80H$_{2\%}$ formulations gave 94.3%, 92.36% and 89.27% of drug release for 24 hrs respectively,This may be due to an increased wettability of the drug by using such hydrophilic carriers and an increased amount of the drug being available for dissolution as cyclodextrins have been found to enhance the permeation by increasing the aqueous solubility of ibuprofen.[34] Since HPβ-CD is more hydrophilic than β-CD and has an aqueous solubility in excess of 50% (w/v), it forms stronger inclusion complexes to allow IB to readily penetrate into the skin.[35] Other studies have shown the suitability of CDs as transdermal delivery carriers due to their ability to enhance permeation without inducing physiological changes in the skin.[36,37]

The expected log P value of 1.3 was obtained with a drug:HpβCD ratio of 1:0.5. Table 3 depicts the log P values of various proportions of the drug and the HpβCD carrier used in preparation. HPβ-CD was further studied as it was found to display properties characteristic of a permeation enhancer. Drug complexes with low log P values are hydrophilic and may have difficulty permeating the lipids in the stratum corenum. Similarly, permeation is low at high log P values because the lipophilic drug complexes will have poor water solubility, and may accumulate in the skin. Pure ibuprofen's log P value of 4 contributes to its poor skin permeability.[41] Therefore, since extreme P values will cause the drug to be trapped within the stratum corenum, it is integral to have drug complexes exhibiting medium lipophilicity (P value between 1 to 3) for successful transdermal permeation. [38]

It was also observed that the release kinetics of gel showed a higher release (98.21%) for SDIB when compared to pure drug dispersed in gelform and other formulations of SDIB with permeation enhancers (Table 4). SDIBM5% showed comparable release (96.5%) to SDIB (Table 4). The pH of SDIB was found to be 6.2 which may explain its increased permeability as the pHs of the other gels were above 6.2. Since higher pH values increase solubility, but decrease permeability, the pH of SDIB was maintained slightly acidic.[39] As reported in the literature, HPβCD has a permeation enhancing effect when chosen as carrier.[40] Additionally, it is interesting to note that the SDIB formulation without permeation enhancers yielded a higher release rate compared to SDIB in the presence of enhancers like permeation enhancers such as menthol and phospolipon 80H. Such chemical enhancers can be used to improve the bioavailability of topically applied formulations by decreasing the viscosity of the lipids in the stratum corneum [32]. However, they can also alter the intrinsic physiological properties of the skin which may explain their reduced effect on the drug release rate compared to that of SDIB in the absence of enhancers. Therefore, the use of SDIB alone (without enhancers) may improve bioavailability of topically administered IB without affecting the integrity of skin.

The flux was used to gauge the permeation of IB through the skin. Highest flux was obtained for the SDIB formulation in comparison to the IB pure drug and SDIB with penetration enhancers (Table 7). The molecular size and hydrophilic nature of HPβCD-IB complex produced maximum flux by maximizing the amount of free IB available for permeation. The SDIB produced a release of 98.21 % at the end of 8th hour. Since this study requires fast release with a quick onset of action, HPβCD was used to obtain maximum transdermal permeation to result in an expedited pain relief. *In vitro* drug release of IB gel with permeation enhancers such as menthol and phospolipon 80H produced 79.42% and 77.31% drug release within 8 hrs respectively. We also observed that the SDIB flux was higher compared to the other formulations and the formulations with phospolipon as a permeation enhancer had a flux as comparable to that of the SDIB formulation (Table 7).

We also found that the SDIB formulation has the most potent anti-inflammatory effect as it minimized skin edema compared to all other formulations. The percentage inhibitions of the edema formation by the gels were in the range of 18.32% to 67.96% and the maximum inhibition was shown by the SDIB formulation (Table 8). Here, the inhibition of edema was used to ensure retention of the functional efficacy of SDIB formulation.

Table 1: Compositions of the gel formulations (%w/w)

INGREDIENTS	IB	SDIB	IBIPM 5%	IBIPM 10 %	SDIBIPM 5%	SDIBIPM 10 %	IBPL 80H 1%	IBPL 80H 2%	IBPL 80H 2.5 %	SDIBPL 80H 1%	SDIBPL 80H 2%	SDIBPL 80H 2.5%	IBM 5%	IBM 10 %	SDIBM 5%	SDIBM 10%
IB (%w/w)	1	-	1	1	-	-	1	1	1	-	-	-	1	1	-	-
SDIB (EQ)	-	1	-	-	1	1	-	-	-	1	1	1	-	-	1	1
Carbopol 941(%w/w)	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Alcohol	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Propylene glycol (%w/v)	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Isopropyl myristate (%w/v)	-	-	5	10	5	10	-	-	-	-	-	-	-	-	-	-
Phospolipon 80H (%w/w)	-	-	-	-	-	-	1	2	2.5	1	2	2.5	-	-	-	-
Menthol (%w/w)	-	-	-	-	-	-	-	-	-	-	-	-	5	10	5	10
Triethanolamine (ml)	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7
Sodium chloride (%w/w)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Water (ml)	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14

Note: IB – plain IB gel; SDIB- solid dispersion of IB; IBIPM- IB with Isopropyl Myristate; SDIBIPM- Solid dispersion of IB with Isopropyl Myristate; IBPL 80h- IB with Phospolipon 80h; SDIBPL 80h- Solid dispersion of IB with Phospolipon 80h; IBM- IB with Menthol; SDIBM- solid dispersion of IB with menthol.

Table 2: Percentage release profiles of IB with HP β CD as carrier in 7.4 pH phosphate buffer

Time (mins)	PD (1%W/W)	1:0.5 (HPβCD)	1:1 (HPβ-CD)	1:2 (HPβ-CD)	1:3 (HPβ-CD)
0	0	0	0	0	0
5	10.21	17.51	37.26	40.63	48.63
10	10.35	22.57	49.87	54.93	60.41
15	10.61	34.28	58.92	68.04	72.6
30	11.03	46.49	66.43	78.00	80.39
45	11.64	53.20	79.41	82.83	96.21
60	12.45	72.58	89.30	94.89	99.98

Table 3: Partition coefficient of optimized IB solid dispersions

Drug: Polymer	Aqueous phase	Organic phase	Log P
1:0.5	0.589	14.130	1.3
1:1	1.059	11.412	0.990
1:2	0.959	7.705	0.904
1:3	0.5	4.102	0.853
1:4	1.038	3.547	0.399

Table 4: Comparative in vitro release profile of ibuprofen with solid dispersion incorporated in gel and with permeation enhancers

TIME (hrs)	IB	SDIB	IBIPM$_{5\%}$	IBIPM$_{1\%}$	SDIB IPM$_{5\%}$	SDIB IPM$_{10\%}$	IB PL80H$_{1\%}$	IB PL80H$_{2\%}$
0	0	0	0	0	0	0	0	0
0.16	0.62	2.6	1.6	1.72	1.64	1.48	1.06	1.82
0.5	2.088	8.59	4.8	3.62	4.51	3.91	3.2	3.91
60	2.345	20.02	5.11	4.89	5.25	4.26	3.8	5.6
120	3.68	44.82	6.24	9.62	6.8	8.46	4.6	7.82
180	8.86	55.75	13.80	12.68	14.04	12.83	8.2	15.05
240	10.69	64.37	26.45	18.31	29.7	16.09	15.6	28.16
300	13.11	76.8	30.89	21.92	34.3	19.59	20.3	34.2
360	14.71	81.23	32.44	26.46	44.36	24.58	38.3	47.42
420	16.58	93.67	35.93	31.39	49.20	29.94	46.1	52.72
480	19.02	98.21	39.35	36.16	51.4	34.51	58.2	76.31

Table 5: Comparative in vitro release profile of IB with solid dispersion incorporated in gel and with permeation enhancers.

TIME (min)	IB PL80H$_{2.5\%}$	SDIB PL80H$_{1\%}$	SDIB PL80H$_{2\%}$	SDIB PL80H$_{2.5\%}$	IBM $_{5\%}$	IBM$_{10\%}$	SDIB M$_{5\%}$	SDIB M$_{10\%}$
0.16	1.14	1.2	2.05	1.19	1.46	1.59	2.5	1.9
0.5	2.16	3.2	4.2	2.42	3.18	3.60	8.36	6.32
60	2.69	4.9	6.9	2.86	9.1	10.0	19.39	16.04
120	3.86	7.9	8.3	3.75	20.6	19.41	40.92	29.38
180	7.9	13.9	22.6	6.92	29.46	27.73	56.5	38.19
240	11.4	25.33	30.5	10.06	35.8	33	63.2	46.31
300	16.49	33.23	38.6	15.31	47.2	41.8	74.62	55.16
360	26.32	46.45	50.5	28.56	56.19	50.3	80.19	69.01
420	34.5	51.3	64.5	33.29	63.48	57.6	86.42	73.59
480	36.7	57.6	82.1	37.26	79.42	61.2	96.5	78.5

Table 6: Ex vivo drug release of IB gel optimized formulations

Time (hrs)	IB	SDIB	SDIB IPM $_{5\%}$	SDIB M $_{5\%}$	SDIB PL80H$_{2\%}$
0.166	0.17	1.86	1.21	1.62	1.95
0.5	0.33	3.92	1.816	2.06	4.02
1	1.26	8.16	2.35	4.97	7.96
2	1.84	17.57	4.36	11.85	9.62
3	2.35	26.91	8.13	19.23	20.08
4	3.4	42.19	14.46	37.52	38.27
5	3.64	51.48	21.57	43.143	51.55
6	3.65	62.69	29.31	53.57	54.83
7	4.35	70.02	36.55	60.92	59.12
8	9.76	74.67	41.59	68.38	63.73
9	12.29	77.18	45.20	71.54	67.45
10	13.98	79.69	50.23	74.93	71.38
21	24.89	91.2	68.14	89.984	84.12
24	26.08	94.3	74.19	92.36	89.27

Table 7: Ex-vivo drug release of IB gel flux and permeability coefficient

Formulation code	Flux (j) (mcg/cm^2/hr)	Permeability coefficient (Kp) (cm^2/hr)
IB	0.5	0.1
SDIB	2.5	0.5
$IPM_{5\%}$	1.1	0.3
$SDIPM_{5\%}$	1.4	0.4
$IBPL_{2\%}$	2.1	0.5
$SDIBPL_{2\%}$	2.0	0.4
$IBM_{5\%}$	2.0	0.4
$SDIBM_{5\%}$	2.4	0.5

Table 8: Percentage protection against edema formation

Formulation	30 mins	60 mins	120 mins	180 mins
SD	40%	42%	55.55%	72.83%
IB	4.5%	8.25%	14.62%	18.32%
SDIB	25%	34.21%	41.67%	67.96%
$SD_{IPM5\%}$	11.25%	15.17%	26.51%	33.19%
$SDIB_{M5\%}$	16.15%	23.36%	34.09%	41.20%
$SDIB_{PL80H2\%}$	19.32%	26.15%	38.18%	45.51%

Note: SD = Standard

CONCLUSION

There is an increased need for topical forms of ibuprufen due to the gastrointestinal and liver problems, which can manifest in patients taking oral forms of the drug, since topical drug delivery system bypasses the GI system, and first pass metabolism by the liver. The disadvantages like first pass metabolism, poor absorption though skin can be overcome by topical drug delivery system. Ibuprofen possessing similar disadvantage was manipulated and additionally, SDIB is a better alternative to improve the solubility and penetration through the skin.

Future studies may involve studying the analgesic effects of SDIB formulation to explore a possible safe alternative to narcotics. Therefore, the ease and safety of transdermal delivery of IB makes it a potentially ideal drug delivery system to produce analgesic and anti-inflammatory effect thus reducing the systemic adverse effects.

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