International Journal of Pharma and Bio Sciences

FORMULATION & EVALUATION OF MELOXICAM SOLID DISPERSION INCORPORATED TOPICAL GELS

M.A.SALEEM* AND SUMANJI BALA

Department of pharmaceutics, Luqman College of pharmacy, Gulbarga, India.

**** Corresponding Author*** ssaleempharm@rediffmail.com

ABSTRACT

Solid dispersion complexes of meloxicam were prepared by using cyclodextrins (BCD, HPBCD), PVP and urea by kneading method in different molar and weight ratios. The complexes were characterized by DSC and IR, suggested that no chemical interaction between drug and carrier. The solubility, dissolution and permeability was studied for prepared complexes. The solubility, dissolution and permeability of complexes was markedly increased as compared to pure drug. Solid complexes were incorporated in 1% carbopol to prepare gels and evaluated for pH ,drug content, viscosity, *invitro* permeability through rat skin . *Invitro* permeation study reveals that the flux (Jss) and enhancement factor increases with increase in concentration of BCD, HPBCD and decreased dramatically in case of HPBCD with ratio of 1:2. Similar changes in pattern of permeation were observed with urea and PVP complexes .Hence it can be concluded that solid dispersion complex incorporated gel shows highest permeation as compared to plain drug gels.

KEYWORDS

Meloxicam, Cyclodextrin, PVP, Urea, Permeability, dissolution.

INTRODUCTION

NSAIDs have been widely used in the treatment of rheumatoid arthritis and other related condition .However, they carry the risk of undesirable systemic side effect and gastrointestinal irritation at the usual dose of oral administration[1] .Considering the fact that most inflammatory diseases occur locally and near the surface of the body ,topical application of NSAID on the inflamed site can offer the advantage of delivering a drug directly to the disease site and producing its local effect .This occurs by avoiding gastric irritation and also reduced adverse systemic effect[2,3] .However the barrier properties of intact skin limit the permeability of wide variety of substance including pharmaceutical active agent.

Meloxicam, a potent NSAID is a preferential inhibitor of cyclooxygenase -2 and has analgesic and anti-inflammatory activity, widely used in the treatment of rheumatoid arthritis, osteoarthritis and other joint disease. The poor aqueous solubility and wettability of meloxicam leads to difficulty in formulating oral and topical formulation. Therefore a better oral or topical formulation can be developed by increasing the water solubility of drugs. The formation of solid dispersion is an effective method for increasing the dissolution rate of poorly soluble drugs, hence improving their bioavailability[4].The literature survey reveals that the solubility of meloxicam can be enhanced by

solid dispersion using cyclodextrins and PVP[5,6].Cyclodextrin have reported to modified transdermal drug penetration of many compound by complexation and accelerate drug release by enhancing the proportion of diffusible substance.Cyclodextrin and their complexes act as a true carrier ,by keeping the poorly soluble drug molecule in solution and helps in penetration[7,8]. Polyvinyl pyrolidon (PVP) is well tolerated physiologically, readily soluble in water and has been used for increasing the solubility, dissolution and permeability[6]. Urea is a hydrating agent, form solid dispersion, improve the solubility and dissolution of poorly soluble drugs and promotes transdermal permeation by facilitating the hydration of stratum corneum [9].

Hence, the present work has undertaken to develop solid dispersion using CDs, PVP and urea in order to improve solubility, dissolution and permeability. The complexes were incorporated in 1% carbopol to prepare topical gel with better patient compliance.

MATERIALS AND METHODS

Meloxicam was kindly provided as gift sample from Alcon Bioscience Pvt. Ltd.Vapi, Gujarat, India. PVP was obtained from Loba Chemie Ltd. Mumbai, India and urea from SD Fine Chem. Ltd. Mumbai. All other chemicals used were of analytical grade.

(i) Development of solid dispersion.

The binary system of meloxicam and cyclodextrins (BCD, HPBCD) were prepared in 1:1 and 1:2 molar ratios in water : methanol (1:1 v/v) solution by kneading method. Solid dispersion of meloxicam were prepared with PVP in weight ratios of 1:1, 1:3 and 1:5 using kneading method with a small volume of methylene chloride. The solid dispersions of meloxicam with urea were also prepared in weight ratios of 1:1, 1:3 and 1:5 using mixture of ethanol/ chloroform as solvent. The prepared slurry obtained in all above methods were dried, crushed and sieved.

(iii) Characterization of solid dispersion.

The infrared (IR) spectra and differential scanning calorimetery (DSC) thermogram were recorded for selected solid system such as B1,H2, P3 and U3. The IR spectra was recorded by FT-IR (Perkin Elmer Instrument USA 16PC) using KBR disc method, the sample were scanned over the range of 4000 to 450 cm^{-1}. For DSC studies each selected sample weighing in the range of 3 to 5 mg were scanned at rate of 10º/min on Shimadzu DSC TA 60 WS Thermal Analyzer between 30º to 300º.

(iv) Evaluation of meloxicam solid dispersion for solubility, dissolution and permeability.

Solubility studies was carried out by taking excess amount of solid dispersion in 3 ml of phosphate buffer pH 7.4 and distilled water, sonicate for one hour and maintained at temperature 37º for 72 h.

The dissolution study was conducted by using dissolution apparatus USP XXIII (Electro lab). The dissolution medium was 900 ml phosphate buffer pH 7.4 maintained at 37±0.5º temperature stirred at the rate of 50 rpm. At appropriate interval 5 ml sample was withdrawn, and analyzed.

The permeation study was conducted by using rat abdominal skin in 100 ml phosphate buffer pH 7.4. Skin was obtained from male rat weighing 140-160 g after approval from institutional ethics committee (No. 346/ CPCSEA). Skin (0.025 cm) was stretched over one end of an open-ended glass tube[12]. The surface area available for the diffusion was 1.76 cm^2 and maintained at 37º using hot plate magnetic stirrer maintained at 50 rpm. A 3 ml aliquot of saturated phosphate buffer pH 7.4 solution of pure drug and solid dispersion was inserted into the tube[6]. At time interval (up to 6 h) sample (5 ml) were removed from receptor compartment and analyzed spectrophotometrically at 362 nm by using Shimadzu UV-visible spectrophotometer.

(vii) Formulations of meloxicam gel.

The prepared solid dispersion equivalent to 300 mg meloxicam and pure drug was dissolved in water. Carbopol 940 in 1% w/w ratio was soaked in required amount of water along with drug solution and then neutralized by triethanolamine.

Table 2.
Formulation of meloxicam gel with different meloxicam solid dispersion.

Ingredient (% w/w)	Formulation Code										
	MG	B1G	B2G	H1G	H2G	P1G	P3G	P5G	U1G	U3G	U5G
Meloxicam	0.30	--	--	--	--	--	--	--	--	--	--
Solid complex	--	1.26	2.23	1.77	2.66	0.60	1.20	1.80	0.60	1.20	1.80
Carbopol	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Triethanolamine(qs)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Water (q.s)	98.57	97.61	96.64	97.11	96.22	98.27	97.67	97.87	96.22	98.27	97.07

MG= Plain gel, B1G and B2G= gels containing meloxicam: BCD in 1:1 and 1:2 ratio, H1G and H2G= gels containing meloxicam: HPBCD in 1:1 and 1:2 ratio, P1G, P3G and P5G= gels containing meloxicam: PVP in 1:1, 1:3 and 1:5 ratio, U1G, U3G and U5G= gels containing meloxicam: urea in 1:1, 1:3 and 1:5 ratio

(viii) Evaluation of gels for pH, drug content and viscosity.

One gram of the gel formulation was dispersed in 10 ml of distilled water and the pH was determined by digital pen pH meter.

Drug content was determined by taking required quantity of gel equal to 10 mg meloxicam and transferred to 100 ml of volumetric flask containing phosphate buffer pH 7.4 , it allowed to sonicate and filtered, from which 1 ml of aliquot was pipette out and diluted to 10 ml. The content of meloxicam was determined by using Shimadzu UV-visible spectrophotometer at 362 nm against blank.

The viscosity was determined by using Brookfield LVDV-III ultra programmable rheometer with spindle No.CP-52 with an optimum speed of 2 rpm.

(ix) *In vitro* permeation study[11]

The rate and extent of skin permeation of meloxicam from gel formulation was determined using a modified glass diffusion cell fitted with abdominal rat skin. Skin was stretched over the end of an open-ended glass tube such that stratum corneum side facing upward into donor compartment and the dermal facing downward into receptor compartment .The donor cell was filled with 3.33gm of gel formulation equivalent to 10 mg of meloxicam such that preparation occupies inner circumference of the tube and immersed in diffusion medium 100 ml of phosphate buffer pH 7.4, diffusion medium maintained at 37±2º. The medium were stirred using hot plate magnetic stirrer at 50±5 rpm. The surface area available for the diffusion was 1.76 cm^2. A quantity of 5 ml of receptor medium was withdrawn at different time intervals and replaced immediately with an equal volume of receptor solution to maintain a constant volume. The release drug was estimated by using Shimadzu UV-visible spectrophotometer at 362 nm.

RESULTS

IR Spectra of pure drug meloxicam and selected meloxicam solid dispersion.

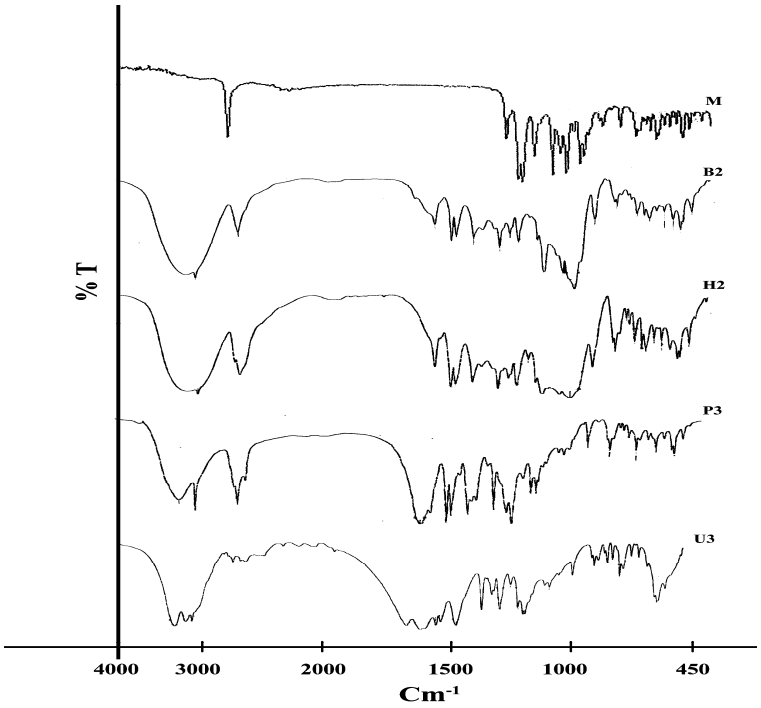

Figure 1 IR Spectra of pure meloxicam (M); meloxicam and BCD solid dispersion 1:2(B2); meloxicam and HPBCD solid dispersion 1:2 (H2) ; meloxicam and PVP solid dispersion 1:3 (P3) ; meloxicam and urea solid dispersion 1:3 (U3) .

DSC thermogram of pure drug meloxicam and selected meloxicam solid dispersion.

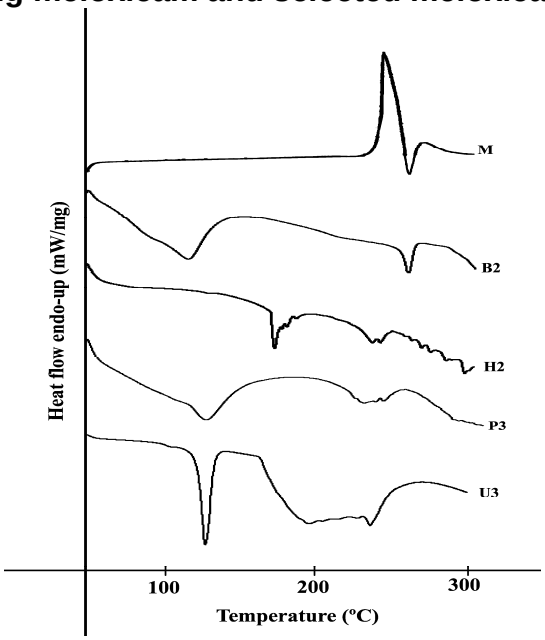

Figure 2 DSC thermogram of pure meloxicam (M); meloxicam and BCD solid dispersion 1:2(B2); meloxicam and HPBCD solid dispersion 1:2(H2) ; meloxicam and PVP solid dispersion 1:3 (P3) ; meloxicam and urea solid dispersion 1:3(U3) .

Table 1

Evaluation of solubility and permeability of meloxicam solid dispersion.

Formulation Code	Solubility (mg/ml) *		Permeability rate * (µg/cm²/hr)
	Phosphate buffer pH 7.4	Water	
Pure drug	0.398±0.35	0.011±0.23	91.92±0.13
B1	2.653±0.65	0.487±0.33	425.38±0.44
B2	2.790±0.45	1.046±0.34	560.86±0.93
H1	3.683±0.55	1.845±0.37	799.25±0.56
H2	2.608±0.70	1.636±0.40	688.06±0.29
P1	1.251±0.65	0.640±0.45	105.02±0.75
P3	1.738±0.45	1.329±0.37	136.36±0.81
P5	1.768±0.35	1.515±0.43	155.34±0.57
U1	0.996±0.43	0.284±0.53	100.19±0.59
U3	1.056±0.25	0.296±0.62	109.56±0.48
U5	1.190±0.15	0.355±0.71	119.73±0.98

*(mean±SD, n=3)

Dissolution profile of pure drug and solid dispersion in phosphate buffer pH 7.4.

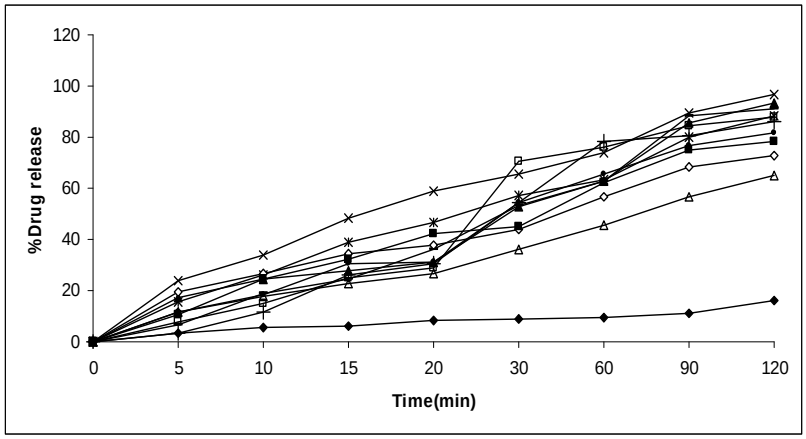

Figure 3 Dissolution profile shows increase in dissolution rate as the concentration of carriers was increased in weight ratio.

Dissolution profile of meloxicam M (–⬧–) ; meloxicam : BCD complex in 1:1 (–□–) and 1:2 (–▲–) ; meloxicam : HPBCD complex in 1:1 (–x–) and 1:2 (––) ; meloxicam : PVP complex in 1:1 (–●–), 1:3 (–|–), 1:5 (–□–) ; meloxicam and urea 1:1 (–△–), 1:3 (–◇–) and 1:5 (–■–) .*

Table 3.

Evaluation parameter of meloxicam gel.

Formulation Code	pH *	Drug content (%)*	Viscosity(cps) *
MG	6.3±0.15	96.58±0.54	7413.43±102.13
B1G	6.9±0.15	90.50±0.35	5328.44±113.14
B2G	6.9±0.05	98.02±0.70	5200.00±161.24
H1G	6.1±0.20	91.40±0.20	3152.18±113.12
H2G	6.3±0.08	92.25±0.40	4954.90±104.13
P1G	6.2±0.11	90.60±0.38	6125.11±126.11
P3G	6.1±0.20	90.31±0.07	5416.42±115.12
P5G	6.2±0.05	93.31±0.15	7177.37±112.3
U1G	6.3±0.10	94.68±0.23	7157.10±107.13
U3G	6.4±0.05	99.24±0.34	5221.50±115.10
U5G	6.4±0.20	98.63±0.15	7323.44±116.14

*(mean±SD, n=3)

Table 4.

Percutaneous permeation parameters of meloxicam gel through rat skin.

Formulation code	Amount permeated at 6 hr, Q_6 (µg/cm²)	Flux, Jss (µg/cm²/h)	*Enhancement factor	Lag time, t_L (h)	Permeability coefficient, K_P (cm/h x 10^{-2})	Diffusion coefficient, D (cm²/h x 10^{-4})	Partition coefficient (K)	Release rate constant, k (µg/cm²/$h^{0.5}$)
MG	485.04	82.04	1.0	0.11	0.82	8.9	0.22	199.49
B1G	3261.54	510.81	6.2	0.39	5.10	2.60	4.88	1226.19
B2G	3565.69	583.85	7.1	0.26	5.80	3.90	3.67	1419.34
H1G	4445.79	783.76	9.55	0.28	7.80	3.60	5.39	1901.30
H2G	3811.60	642.23	7.82	0.21	6.40	4.29	3.20	1572.70
P1G	2135.53	375.52	4.57	0.66	3.70	1.50	5.90	878.51
P3G	3183.88	611.16	7.44	0.30	6.10	3.40	4.40	1508.07
P5G	2892.67	488.81	5.90	0.40	4.88	2.57	4.75	1166.62
U1G	1676.07	279.97	3.41	0.64	2.70	1.60	4.36	651.64
U3G	3306.84	621.70	7.50	0.57	6.21	1.79	8.64	1474.09
U5G	2148.47	384.90	4.69	0.62	3.80	1.67	5.70	900.78

$$*\text{Enhancement factor} = \frac{\text{Flux with carrier}}{\text{Flux without carrier}}$$

Comparative permeation profile of meloxicam in phosphate buffer pH 7.4 from plain drug gel with gels containing solid dispersion.

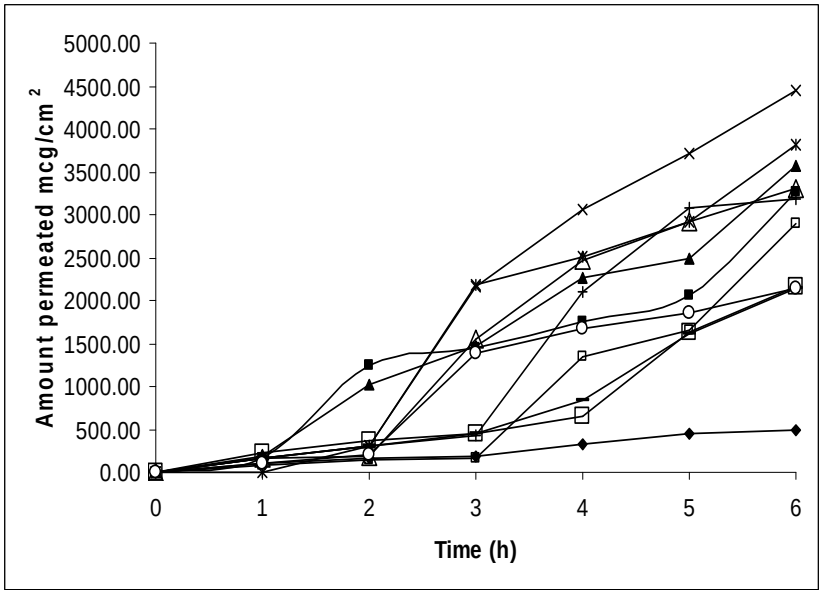

Figure 4. *Plain gel MG (–♦–), gel containing meloxicam: BCD solid dispersion in 1:1 B1G (–■–) and 1:2 B2G (–▲–); meloxicam: HPBCD solid dispersion in 1:1 H1G (–×–) and 1:2 H2G (–*–). , gel containing meloxicam: PVP solid dispersion in1:1 P1G (–□–), 1:3 P3G (– +–) and 1:5 P5G (–▫–); gel containing meloxicam and urea solid dispersion 1:1 U1G (–□–), 1:3 U3G (–Δ–) and 1:5 U5G (–○–).*

DISCUSSIONS

In the present work meloxicam was complex with highly water soluble carrier like cyclodextrin, PVP and urea .Meloxicam was complex with BCD and HPBCD in molar ratio 1:1, 1:2 where as PVP and urea complexes were prepared in the weight ratio of 1:1, 1:3, 1:5 by kneading method. The solid dispersion was characterized by IR and DSC. IR and Thermal behavior of pure drug and some selected drug carrier complexes depicted in fig (1&2). IR studies indicate that there is only physical entrapment of meloxicam with carrier molecule .The DSC thermo gram of pure meloxicam and carrier complex shows sharp endotherm followed by exotherm which signifies that after melting meloxicam decomposes, indicating some crystal of pure meloxicam kept there in crystalline nature.

The solubility studies were carried out in both distilled water and phosphate buffer pH 7.4 presented in Table 1 shows increased solubility either in molar ratio for CDs or in weight ratios for PVP and urea except the formulation H2, which shows decrease in solubility due to increased viscosity and saturation of solution. *In vitro* dissolution study (Fig 3) show the dissolution of solid dispersion was more than 60% within 120 min as compared to pure meloxicam which shows only 15.85% of drug release. The highest percent drug dissolution was observed with CD complexes (more than 90%) as compared to PVP and urea. The *in vitro* drug release was increased in the manner of pure drug < urea < PVP < BCD< HPBCD. The results of *in vitro* dissolution study were correlated with the solubility study.

The amount of drug permeated (µg/cm²/h) through rat skin during the time course of 6 h depicted in Table1, indicated that solid dispersion increase the overall meloxicam diffusion by increasing the amount of diffusion species in donor phase by enhancing drug solubility. The highest permeation was observed with H1 formulation as compared to other formulation. The amount permeated was increased with respect to each carrier as the concentration of carrier was increased except in H2 formulation which shows a decrease permeation, might be due to increase viscosity in the of solution in donor phase. The findings of permeation study fully supported the solubility and dissolution study. Based on the permeability study perform for the solid dispersion it was observed that carrier used in the study results in increased permeation of meloxicam and hence the meloxicam solid dispersion were incorporated in 1% carbopol 940 to prepare gel formulation.

All the prepared gels were subjected to evaluation for pH, content uniformity, viscosity and the data is presented in Table 3. The pH of all formulation was more than 6.0, which lies in the normal skin pH. The drug content was in the range of 91.4% to 99.24% indicating uniform dispersion of meloxicam in the gels, all formulated gel showed an increase in the viscosity as the amount of carrier was increased. The *in vitro* percent drug release of meloxicam through rat skin was found to be more for solid dispersion gels as compared to plain drug gel. This was due to more solubility, highest dissolution of solid dispersion as compared to pure meloxicam. The *in vitro* release was in the order of HPBCD gel>BCD gel> PVP gel> urea gel>plain gel. All the percutaneous parameters through rat skin were calculated and presented in Table 4. The gel H1G shows highest flux of 783.769 µg/cm²/h with enhancement factor of 9.5. The result shows that permeation rate of meloxicam was increased significantly ($p<0.05$) for cyclodextrin gel formulation as compared to plain drug gel, which shows flux of only 82.047 µg/cm²/h. In the HPBCD gel formulation H_2G shows decrease flux as the molar concentration of HPBCD was increased. In BCD gel formulation, the permeation rate was increased as the molar concentration of BCD was increased. These results confirmed the conclusion of previous literature. The cyclodextrin might act as permeation enhancer by transfering the drug from the solution towards lipophilic surface of biological membrane when the drug molecule distributed from the complex into the membrane. The complex does not penetrate the skin, the drug in the complex is in rapid dynamic equilibrium with drug in the aqueous phase, thus continuously supplying the drug molecule to skin surface in diffusible form. The lipophilic

drug in the cavity of cyclodextrin, partition into membrane (skin) for which they have a greater affinity. In HPBCD formulation as molar concentration of HPBCD increased would decrease the amount of free drug and reduce the penetration flux through skin.

The flux obtained form PVP gel formulation P1G, P3G, P5G, was 375.521 μg/cm²/h, 611.16 μg/cm²/h, 488.81 μg/cm²/h, with the enhancement factor of 4.5, 7.4, and 5.9 respectively. The permeation rate was significantly increased ($p<0.05$) as compared to plain drug gel. The increase flux which suggests that PVP might possess a role in penetration enhancer that appears as using viable membrane. The mechanism involve decrease particle size of drug, increase wettability and preventing the aggregation of drug by PVP as it shows enhanced dissolution rate. The decrease flux in P_5G formulation as the concentration of PVP increased might be due to increase in the viscosity in the donor phase.

The flux obtained for urea gel formulation U1G, U3G, U5G was found to 279.97 μg/cm²/h, 621.708 μg/cm²/h, 384.90 μg/cm²/h with the enhancement factor of 3.4, 7.5 and 4.6 respectively. The permeation rate was more as compared to plain drug gel. The flux obtained for U5G was less as compared to U3G which might be due to an increase in viscosity of solution in the donor phase. The permeation rate was more as compared to plain drug gel. Urea act as a penetration enhancer as hydrating agent and keratolytic agent, which could affect the stratum corneum corneocytes, this action lead to believe that it would increase the penetration of drug through the skin.

CONCLUSION

The solubility, dissolution and permeability was significantly enhanced by using solid dispersions of meloxicam .Hence meloxicam solid dispersion incorporated gel shows highest drug permeation through rat skin as compared to plain drug gel.

REFERENCES

1. Rafice Tehrani M and Mehramizi A, In vitro release studies of piroxicam from oil in water creams and hydro alcoholic topical gel formulation, Drug Dev .Ind.Pharm , 26(4) : 409- 414,(1996).
2. Arellano A, Santoyo S, Martin C and Ygartua P, Influence of propylene glycol and isopropyl myristate on the in vitro percutaneous penetration of diclofenac sodium from carbopol gels, Eur.J.Pharm. Sci, 7 (2): 129 – 135, (1999).
3. Arellano A,Santoyo S, Martin C and Ygartua P, Surfactant effect on the in vitro percutaneous absorption of diclofenac sodium.Eur.J.Drug .Metab.Pharmacokinet, 23 (2):307 – 312, (1998).
4. El- Gazayerly ON, Characterization and evaluation of tenoxicam co precipitate, Drug .Dev .Ind.Pharm 26,925-930, (2000).
5. Buchi Naidu N, Chowdary KPR, Murthy KVR, Satyanarayana V, Hayman AR, Physicochemical characterization and dissolution properties of meloxicam – cyclodextrin binary system. Journal of Pharmaceutical & Biomedical Analysis, 35: 75-86, (2004).
6. El-Badry M, Fathy M, Enhancement of the dissolution and permeation rate of meloxicam by formulation of its freeze-dried solid dispersion in PVPK-30. Drug Development & Industrial Pharmacy, 32: 141-150, (2006).
7. Loftson M and Masson M, Cyclodextrin in topical drug formulation; theory and practice, Int .J.Pharm, 225:15-30, (2001).
8. Masson M, Loftson T, Masson G, Stefansson E, Cyclodextrin as permeation enhancers: Some theoretical evaluation and invitro testing .J.Control Release, 59:107-118, (1999).
9. William C. Adrian, Barry W.Brain, Penetration enhancer. Advances Drug Delivery Review, 56: 603-618, (2004).
10. Santoyo S, Arellano A, Ygartua P, Martin C, In vitro percutaneous absorption of piroxicam through synthetic membrane and abdominal rat skin. Pharmaceutic Acta Helvetica, 71: 141-146, (1996).
11. Zuber M, Chemtob C and Chaumeli JC, Invitro availability of a topical corticosteroid from various vehicles. Attempt at correlation with an in vitro

study.J.Pharm.Belg.37 96):393-400, (1982).