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FORMULATION AND EVALUATION OF POLYMERIC MICELLE DRUG DELIVERY SYSTEM OF CELECOXIB TO IMPROVE THE ORAL ABSORPTION

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ABSTRACT

Purpose: The aim of this study was to formulate polymeric micelle systemcontaining a lipophilic drug, celecoxib, and to explore the potential of carriers for such system. **Methods:** Full factorial design with three variables; drug percentage, type of surfactant mixture and co surfactant amount in two levels were used. The effects of variables on formulation characters; particle size, drug release and permeability from rat intestine were evaluated. **Results:** All formulations with particle size between 7.63 to 97.66 nm significantly increased celecoxib aqueous solubility that this effect is dependent to surfactant mixture. The results showed oleic acid as oil, labrafil -labrasol and Poloxamer - propylene glycol as surfactant mixtures, Capryol 90 as co-surfactant and lecithin as oily phase and membrane stabilizer agent prepared stable micellar formulations with sustained release property. Percent of drug release after 24 hrs. (% DR_{24}) was between 11.95 to 46.82. All polymeric micelle formulations increased drug permeated through rat intestine. Maximum increase in p_4 was 39.12 times compared to control. The result shows that drug percent and co surfactant amounthave a significant relationshipwith % P4. ($p \leq 0.05$). All drug formulations containing 3% of drug, as compared to formulations containing 1% have a higher rate of gastrointestinal absorption. **Conclusion:** All formulations indicated sustained release profiles. Drug permeability through rat intestine was controlled by percent of drug and co surfactant amount in formulations so that higher permeability resulted with higher drug percent and

lower co surfactant amount. This finding may be suggested un saturated intestine absorption of celecoxib.

KEYWORDS: Polymeric micelle systems, Oral absorption, Celecoxib

1. INTRODUCTION

The oral route is one of the most preferred ways for chronic drug therapy; but the drug dissolution is usually a rate-determining step of the absorption processes for poorly water-soluble drugs.The oral route has been several advantages that make it the preferred route of drug administration.[1,2]

Approximately 40% of marketing products are poorly soluble or lipophilic compound that lead to restricted oral bioavailability, high intra and inter subject variability and a possible increase in dose.[3] Celecoxib is a non-steroidal anti-inflammatory drug (NSAID) that acts on cyclooxygenase-2 (COX-2). It has been used extensively to safely treatment patients with arthritis and treatment patients with familial adenomatous polyposis and to induce apoptosis in colon, stomach, prostate cancer cells and have antitumor activity in lung, colon and pancreatic cancer.[4-6]

Celecoxib is a hydrophobic and highly permeable drug belonging to class II of bio pharmaceutics classification system (BCS). It is weakly acidic (pKa is 11.1) and hydrophobic (Log P 3.5) and its low aqueous solubility (3-7 mg/ml) contributes to high variability in absorption after oral administration.[7]

In the case of poorly water-soluble drugs, the dissolution time in the GI contents may be longer than the transit time to the intended absorptive sites.[8] Therefore, dissolution of drugs is quite often the rate-limiting step, which ultimately controls the bioavailability of the drug.[9,10] There are various techniques available to improve the solubility of poorly soluble drugs such as micronization[11], micro emulsification, and novel drug delivery systems, including nanoparticles, lipid-based vesicles, have been proposed.[12] Among the different polymer-based drug delivery systems, polymeric micelles represent a promising delivery vehicle especially intended for poorly water-soluble pharmaceutical active ingredients in order to improve their oral bioavailability. Polymeric micelles can be used as efficient carriers for compounds, which alone exhibit poor solubility, undesired pharmacokinetics, and low stability in a physiological environment.[13]

Typically polymeric micelles are formed from self-aggregation of amphiphilic polymers with the hydrophobic part of the polymer on the inside (core) and hydrophilic on the outside (shell). In polymeric micelle drug delivery systems the core serves as a reservoir for drugs with low aqueous solubility due to the tendency of these drugs to partition into the core as a result of hydrophobic interactions. The hydrophobic core is a key component in determining the micelle's capacity to solubilize a poorly water-soluble compound. The shell of polymeric micelles is composed of the hydrophilic part of the amphiphillic polymer.[14] As a result of theseproperties, the advantages of polymeric micelles as drug delivery systems are two parts: first, the hydrophobic core acts as a solubilization depot for drugs with poor aqueous solubility; second, the hydrophilic shell supplies some protection in limiting opposing adsorption, which contributes towards a longer blood circulation time or better blood stability.[15] Polymeric micelles can increase drug bioavailability and retention, since the drug is well protected from possible inactivation under the effect of their biological medium.The small size of polymeric micelles also contributes towards longer blood circulation time by evading scavenging by the mononuclear phagocyte system in the liver and bypassing the filtration of inter-endothelial cells in the spleen.6 In addition, encapsulation of drug inside the core of polymeric micelle may protect against rapid clearance from circulation, which can lead to reduced amount of drug available for absorption.[15] The aim of this study was to prepare and evaluate of the polymeric micelle formulation for oral delivery of celecoxib.

2. MATERIALS AND METHODS

2.1. Chemicals

Celecoxib was prepared from Exir pharmaceutical Company (Iran). Castor oil Tween 20, Cholesterol, lecithin, Oleic acid, polyethylene glycol (PEG), propyleneglycol (PG) and Poloxamer were obtained from Merck Labrafil, Labrasole, Labrafac, and Capryol 90 were gift from *Gattefosee* Company (France). All chemicals and solvents used in this study were of analytical grade and obtained through commercial sources.

2.2. Animals

Female adult Wistar rats (weighing 250 - 300 g) and aged 10 - 12 weeks were purchased from Animals Laboratory, Jundishapur University of Medical Sciences.

Ahvaz, Iran.The rats were anaesthetized with ether prior to sacrificing them. All rats were sacrificed using chloroform, and then animal intestines were removed completely, divided into four equal parts and then the intestines were washed with cold ringer's solution and their

contents removed. The animals were treated according to the principles for the care and use of laboratory animals, and approval for the animal studies was obtained from the Ethical Committee of Ahvaz Jundishapur University of Medical.

2.3. Celecoxib*assay*

Celecoxib was dissolved in medium containing of 0.1 N hydrochloric acid(HCl), 4%Tween 20(4%) and sodium chloride (0.05%). The amount determination was performed by UV spectrophotometer (Biochrom WPA Bio Wave II) at λmax 257 nm. The validity of assay method involving linearity, repeatability, accuracy, and limit of quantification (LOQ) were calculated.

2.4. Solubility study

The solubility of celecoxib was determined in various oils (Castor oil, oleic acid and Labrafac), surfactant mixtures (labrasol: labrafil(1:1weight ratio) and Poloxamer: water (1:5weight ratio)by dissolving an excess amount of celecoxib in5ml of oil and surfactant mixtures using a stirrer for 30 minutes at 45°C and 24 hours at room temperature. The equilibrated samples were then centrifuged at 6000rpm for 30 min to remove undissolved drug, then the clear supernatant liquid was decanted. The solubility ofcelecoxib was measured by validated UV spectrophotometric method (Biochrom WPA Biowave) at 257nm.[16]

2.5. Preparation of celecoxib polymeric micelleformulations

Several parameters influence on final properties ofcelecoxib polymeric micellar formulations.Major variables take part in polymeric micellar properties includes drug percentage (%drug), cosurfactant amount (a. Cs), and surfactant type(s-type). Full factorial design was used concerning with three variables at two levels forFormulations.Eight different formulations with low and high values of drug percentage (1% and 3%),co surfactant amount (0.015and 0.06 30%), surfactant type (labrasol: labrafil and Poloxamer: water were used for preparing of polymeric micellar formulations,For Preparation of celecoxib polymeric micellar formulations, we has been mixed equal amounts of lecithin, cholesterol , PEG in chloroform. The uniform lipid film was preparedbydryingin rotary evaporator at 120 rpm, 60˚C for 15 min.Aqueous solution containing drug, surfactant (labrasol: labrafil (1:1) or Poloxamer) and co-surfactant (Capryol or PG) have been added to uniform lipid film, sonicated at 25 ˚C. Finally, onegram of the obtained mixture is diluted with 100 ml of distilled water. The compositions of different formulations illustrated in table 1.

2.6. Particle Size Measurement

The mean droplet size of polymeric micellar formulations was measured by SCATTER SCOPE[1] QUIDIX (South Korea) at 25˚C, and their refractory indices were computed.

2.7. Drug release study

Franz diffusion cells (area 3.4618 cm2) with a cellulose membrane (molecular weight G12 000) were used to determine the release rate of celecoxib from different polymeric micellar formulations. The cellulose membrane was first hydrated in distilled water at 25 ºC for 24 hours and then it was clamped between the donor and receptor chambers of the cell diffusion. The receptor compartment wasfilled with 22ml of 0.1 N hydrochloric acid (HCl), 4%Tween 20(4%) and sodium chloride (0.05%). The receptor medium was constantly stirred by externally driven magnetic beads at 300 rpm throughout theexperiment.Celecoxib loaded polymeric micelle formulations (5ml) was accurately weighted and placed in donor compartment. At predetermined time intervals (0.5, 1, 2, 3, 4, 5, 6, 7, 8 and 24h), a 2ml sample was removed from receptor for spectrophotometric determination and replaced immediately with an equal volume of fresh receptor medium.Blank formula (without drug)utilized as control. Samples were analyzed by UV visible spectrophotometer (BioWave II, WPA) at 257 nm.The results were plotted as cumulative released drug percentage versus time.[17]

2.8. Celecoxib Permeability from Rat Intestine

In order to evaluate the permeability of drug from intestine of rat, 0.5 ml of formulation was diluted with 0.5 ml of hydrochloric acid, poured into the intestine and closed from both sides. Then intestine was kept in 30 ml 0.1 N hydrochloric acid, Tween 20(4%) and sodium chloride (0.05%) for 4 hours at 37°C ± 0.5.The sampling was done at 0.5,1, 2, 3, 4-hour time intervals and absorption of the samples was determined by UVvisible spectrophotometer. The same test was carried out for the 1% and 3%suspension of celecoxib as controls. Thus, the amount of passed drugs between polymeric micelle formulation and suspension were compared. Percentage of response to the drug permeated after four hours and the effects of independent variables on it (%) were studied.The results were plotted as cumulative released drug percent.

Versus time Drug release from polymeric micelle formulationshas been explained by fitting on kinetic models in whichcommonly used models such as zero order, first order, Higuchimodels, andthe model with higher r^2 had been selected.[18]

2.9. Critical micelle concentration (CMC) determination

In order to determine Critical micelle concentration for better preparing of micelle formulation we prepared Surfactant and co-surfactant aqueous solutions with different concentrations and the their surface tension were measured at 25˚C with a Torsion balance (WHITE ELEC Model NO. 83944E).Then chart of surface tension versus log concentration was plotted.

2.10. Statistical analysis

All results were expressed, as the mean±standard deviation (SD) and to compare the effect of polymeric micelle formulation and suspension on the amount of permeated drug, $P < 0.05$ was considered statistically significant.The Levene's test was used for homogeneity of variance. In addition, ANOVA and multiple regressions were applied to simultaneously evaluate the relationship between several variables. Minitab 16 software was used for generating and evaluating the experimental design as well as evaluating the effect of variables on responses.

3. RESULTS AND DISCUSSION

3.1. Validity of drug measurement method

The correlation coefficient for the concentration-absorbance was $r^2 = 0.9983$, which means that 99.83% of the absorbance values are estimated by the concentration. Regression analysis showed a significant relationship between concentration and light absorbance ($P = 0.002$). The lackof-fit in this research was not significant ($P = 0.129$), which appears in the estimated absorbance changes. Accuracy of measurement showed those concentrations that were close to the actual values. Repeated surveys accountability in measurement methods within and between days for celecoxib showed the desired repeatability of quantification method on different days and caused nearly-thesameoperation as well as error-free results.

3.2. Solubility study

Solubility studies were done to identify suitable oil phase and surfactant. Among the used oils Labrafac and oleic acid showed minimum and maximum solubility for celecoxib, respectively also insurfactants higher solubility values for Labrasole: Labrafil mixture. Furthermore, oleic acid was chosen as oily phase in polymeric micelle formulations. Solubility of celecoxib in oils and surfactants shown in Table 2.

3.3. Particle size distribution

The polymeric micelle formulations had the mean particle size in the range of 7.63 to 97.66 nm(Table 3).Multivariate regression was used for analyzing the correlation between independentvariables and particle size of polymeric micelle formulations.

The following equation (Eq-1) demonstrates the multivariate regression between independent variables and particle size:

Particle size (PS) = 1.25 + 26.5(%D) – 15(S-type) – 111(a Cs) (Eq-1)

In selected formulations, relationship between particle size with drug percent (p= 0.001) and surfactant type (P =0.001) was significant. The correlations between particle size with drugpercent (%D) was direct and for surfactant type (s-type) was indirect .Thus, the increase in percentage of drug increases the particle size certainly according to lipophilic nature of the drug, this increase was due increases in volume of micelle oil core. In other hand, type of surfactant affected on particle size. Labrasol - Labrafil as surfactant compared to the mixed ploxamr and propylene glycol, was more effective in reducing the particle size.

3.4. Critical Micelle Concentration (CMC) study

Amounts of CMC for surfactant(without surfactant) and surfactant(with co-surfactant)are shown in Table 4.Theresults show that interfacial tension significantly reduced after adding of the Co-surfactant into surfactant. CMC amount of Labrasole –Labrafil surfactantmixture is less than the CMC amount of Poloxamer and propylene glycol. These findingshave been shown that micellestructures can be formed with a lower concentration of Labrasole and Labrafil surfactant mixture. Concentration of mixed surfactants used in formulations designed, was above the CMC of that mixture, so we can conclude that micelles are formed.

3.5. In Vitro Drug Release

The percentage of drug released after 2 hours (%R_2) in the formulations preparedwere From2.66 to 18.53. (Figure 1 and table 5). It seems that due to the lipophilic nature of celecoxib and tends to oily phase; percentage of drug released in the early hours is very low. The following equation (Eq-2) representsthe multivariate regression between independent variables anddrug released after 2 hours:

%R_2=11.4-2.86 (%D) +3.46 (S-type) +86.7 (a Cs)(Eq-2)

In polymeric micelle celecoxib formulations, relationship between % R_2 with drug percent (p= 0.001) and surfactant type (P =0.001) and co surfactant amount (a Cs) (P = 0.002) was

significant as a % R_2 is reduced by increasing the percentage of drug. In other words, the concentration of drug loaded, able to establish a linear relationship with the amount of drug release. On the other hand, surfactant type had a significant effect on the rate of % R_2 in such a way that changing the surfactant mixture from Labrafil - Labrasole to Poloxamer - propylene glycol, increase the amount of drug release after 2 hours.% R_2 is increased by increasing for surfactant.

The percentage of drug released after 24 hours (%R_{24}) in the formulations prepared were from11.95 to 46.82 .The following equation(Eq-3) represents the multivariate regression between independent variables and drug released after 24 hours:

$\%R_{24}=37.9-9.30\ (\%D)+5.36\ (S\text{-type})+229\ (a\ Cs)$(Eq-3)

In polymeric micelle celecoxib formulations, relationship between % R_{24} with drug percent (p= 0.002) and surfactant type (P =0.001) and co surfactant amount (a Cs) (P = 0.004) was significant so that % R2 is increased by reducing in the percentage of drug. On the other hand, surfactant type had a significant effect on the rate of % R_2 in such a way that changing the surfactant mixture from Labrafil - Labrasole to Poloxamer - propylene glycol, may led to increasing the amount of drug release after 2 hours and also % R_2 is increased by increasing in the amount of co surfactant.Percent drug released in 24 hours(%R_{24}) is the symbol of continuous drug release. % R_{24} was 11.95 to 46.82 ranges, that minimum and maximum of % R_{24} belongs to formulation No.7 and 6, respectively. The percentage of drug released and kinetics of release in selected polymeric micelle formulationsare presented in Table 5.

3.6. Celecoxib Permeability from Rat Intestine

The percentage of drug permeability after four hours (%P4) in the selected formulations were from 23.07 to 63.78.(Figure 2 and table 6). The maximum and minimum percentage of drug permeability after four hours (%P_4) was obtained 63.78% (formulation No. 1) in the Labrafil – Labrasole formulations and 23.07(formulation No. 2) in Poloxamer - propylene glycol formulations. The enhancement ratio in the formulation No. 1 was 39.12 times higher than those of saturated water suspension of celecoxib. All polymeric micelle formulations increased drug permeated through rat intestine ($p \leq 0.05$). The following equation (Eq-4) has been shown the multivariate regression between independent variables and percentage of drug permeability after four hours (%P4):

$\%P_4= 28.9 + 10.3(\%D) – 0.90\ (S\text{-type}) - 117(a\ Cs)$ (Eq-4)

The relationship between drug percent (p= 0.001) and co surfactant amount (a Cs) (P = 0.0013)with%$P_4$was significant indicating that in relation to the increased the percent drugand amount of co surfactant , the %P_4 has been increased and decreased , respectively. All drug formulations containing 3% of drug, as compared to formulations containing 1% have a higher rate of gastrointestinal absorption.

Table1.Different Amount of Compounds in the polymeric micelle Formulations of Celecoxib.

formulation	Factorial state	Oleic acid(g)	(Lecithin(g	PEG(g)	Cholestrol(g)	Type of Surfactant	Capryol(g)	Drug (%)	Labrasole(g)	Labrafil(g)	Ploxamer(g)	PG(g)
F1	+-+	3	1	1	1	L+L	0.06	3	0.3	0.3	-	-
F2	--+	3	1	1	1	L+L	0.06	1	0.3	0.3	-	-
F3	+++	3	1	1	1	P+PG	0.06	3	-	-	0.5	0.1
F4	+--	3	1	1	1	L+L	0.015	3	0.15	0.15	-	-
F5	---	3	1	1	1	L+L	0.015	1	0.15	0.15	-	-
F6	-++	3	1	1	1	P+PG	0.015	1	-	-	0.5	0.1
F7	++-	3	1	1	1	P+PG	0.015	3	-	-	0.2	0.1
F8	-+-	3	1	1	1	P+PG	0.015	1	-	-	0.2	0.1

Table 2.The solubility of celecoxib in various oils and surfactants (mg/ml(Mean±SD, n=3)

	Type	Drug Solubility (mg/ml)
Oils	Oleic acid	5.07±0.04
	Castor oil	4.47±0.06
	Labrafac	4.21±0.06
Surfactants	Labrasol:labrafil (1:1)	4.48±0.04
	Poloxamer: Water (1:5)	1.59±0.03

Table 3. Particle size and percentage of drug permeability after one hour (%P_1) and four hours from rat intestine (%P_4) (Mean±SD, n=3)

Formulation No	Factorial design condition	Particle size(nm)	%P_1	%P_4
F1	+ - +	57.43±15.3	42.82±0.55	63.77±1.53
F2	- - +	13.66±4.75	15.3±0.39	28.07±1.35
F3	+ + +	64.66±1.52	32.56±0.52	49.98±1.59
F4	+ - -	92.03±1.95	40.18±0.41	57.55±0.75
F5	---	50.73±2.003	21.76±0.45	41.63±0.88
F6	- + +	7.63±2.06	18.73±0.71	34.58±1.47
F7	+ + -	97.66±2.51	34.4±0.42	49.77±1.15
F8	- + -	22.66±2.51	21.23±0.67	35.09±1.37
Control (1%)	-	-	2.92±0.87	4.45±1.15
Control (3%)	-	-	1.08±0.92	1.63±0.95

Table 4. Amount of CMC for surfactant(without co surfactant), and surfactant(with co-surfactant)(N/ m2)(Mean±SD, n=3)

Surfactants	CMC
Labrasol:labrafil 1:1	0.06
Labrasol:labrafil 1:1 +Capryol90	0.06
Ploxamer	0.16
Ploxamer+Capryol 90	0.06

Table5.Percent Release and kinetic Models Release of Selected polymeric micelle formulations (mean ±SD, n=3)

Formulation	Factorial design condition	% R_2	% R_{24}	Kinetic model	r^2
F1	+ - +	4.65±2.46	16.42±2.91	Higuchi	0.87
F2	- - +	12.14±2.05	35.77±3.91	Higuchi	0.86
F3	+ + +	14.35±0.62	34.1±0.56	Higuchi	0.83
F4	+ - -	2.74±0.47	11.98±0.93	Higuchi	0.86
F5	---	8.5±1.59	26.85±3.30	Higuchi	0.86
F6	- + +	18.53±0.89	46.82±2.70	Higuchi	0.87
F7	+ + -	2.66±0.44	11.95±1.94	Higuchi	0.87
F8	- + -	8.12±1.16	39.43±2.85	Higuchi	0.88

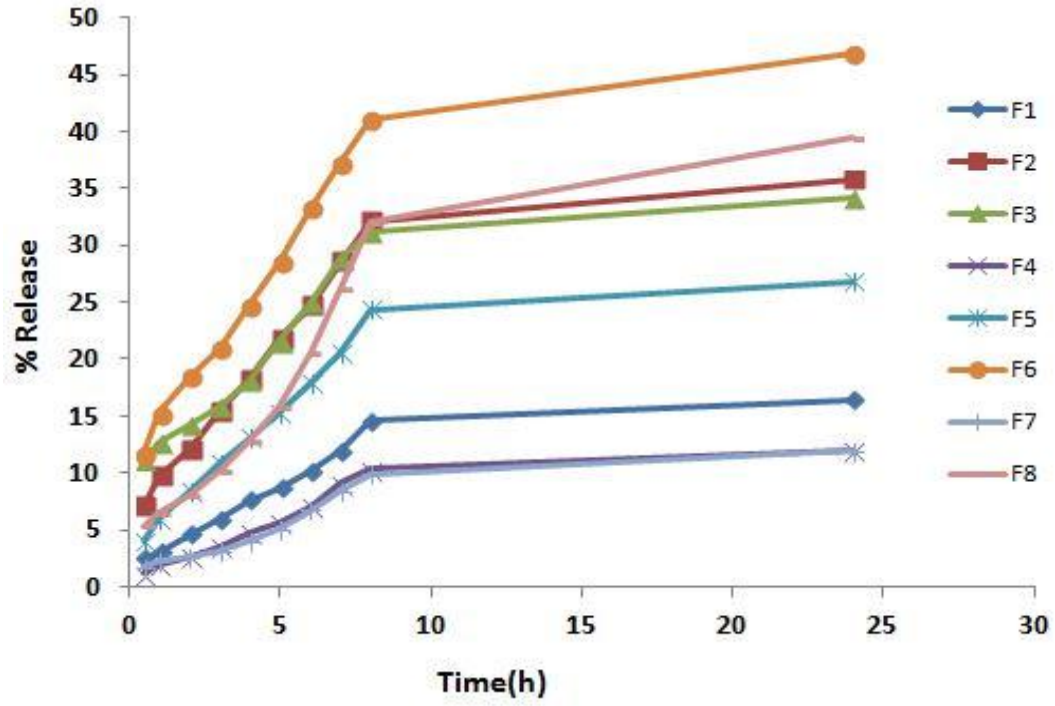

Figure1. In Vitro Release Profile of polymeric micelle Formulations of Celecoxib

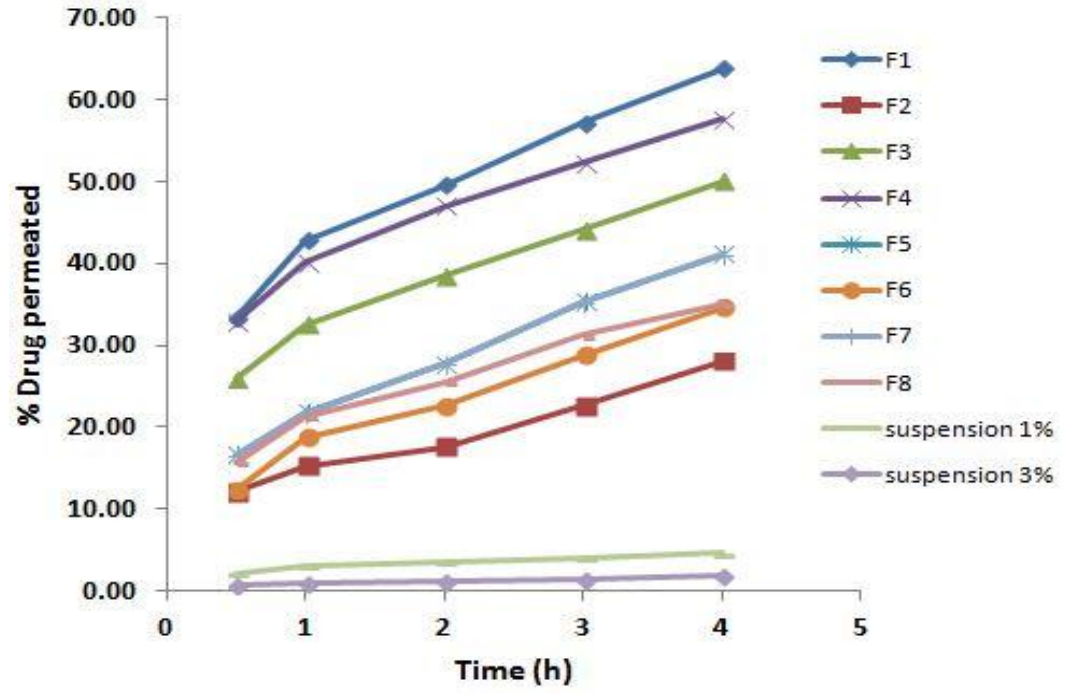

Figure2. In Vitro Celecoxib permeability through the rat intestine from various polymeric micelle formulations and controls.

4. CONCLUSION

The results of this research have been showed that all polymeric micelle formulations increased aqueous solubility and permeability through rat intestine as compare with controls. Micelle formulations composed of labrasol – labrafil surfactant mixture and capryol 90 as cosurfactant, produced micelles with lower CMC and higher particle size as compare with Poloxamer propylene glycol surfactant mixture and the same cosurfactant. Higher drug solubility by labrasol - labrafil is the essential reason for lower drug release percentage as compare with Poloxamer - propylene glycol. The relationship between particle size andpercentage of drug released after 24 hourswas significant indicating that in relation to the decrease the particle size , %R24 increased. All formulations indicated sustained release profiles. Drug permeability through rat intestine was controlled by percent of drug and co surfactant amount informulations so that higher permeability resulted with higher drug percent and lower co surfactant amount. This finding may be suggested UNsaturatedintestine absorption of celecoxib.

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6. AUTHOR'S CONTRIBUTIONS

All authors were involved in all steps of manuscriptpreparation.

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