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Formulation and Evaluation of Diclofenac Organogel

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Abstract

The main objective of current study is to Formulation and evaluation of diclofenac organogel. Diclofenac organogel formulation is optimized and characterized for pH determination, Measurement of viscosity , Globule size, Drug content study and in-vitro drug release study. Effect of different concentration of Span 80, Tween 80 and Sunflower oil on different properties of organogel formulations were studied. In this study, we found all the formulations were in pH range of 7.3-7.5 which is similar to the skin pH and can be topically administered easily. OF2 was found pH 7.4. Viscosity of the formulation was found in the optimum range for the gel preparation. Viscosity of OF2 was found 448 cps at 10 rpm, 202 cps at 20 rpm, 119 cps at 50 rpm, 25 cps at 100 rpm. Globule size was found in 88.00 µm- 110.30 µm size range. Globule size of OF2 was found 98.8 ± 12.33 µm. Formulation was optimized on the basis of drug content study and drug release study and was found that formulation containing 4 gm sunflower oil and having ratio of span 80 and tween 80 1:2 gave the best results. Formulation OF2 was found optimized and ideal formulation exhibited 87.07% drug content and 83.34% drug release.

Keywords: Diclofenac, span 80 , Tween 80 , In- vitro drug release.

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1. Introduction

Inflammation is the attempt of body at self-protection; the aim being to remove harmful stimuli, including damaged cells, irritants, or pathogens - and begin the healing process. When something harmful or irritating affects a part of the body, there is a biological response to try to clear it, the signs and symptoms of inflammation, specifically acute inflammation, shows that the body is trying to heal itself. Inflammation doesn't mean infection, although when an infection causes inflammation. Infection caused by a bacterium, virus or fungus, inflammation is the body's response to it. The word inflammation came from the Latin "inflammo", meaning "I set alight, I ignite". Inflammation is part of response of body's immunity. Initially, it is beneficial when, for eg., your knee sustains a blow and tissues need care and protection. However, sometimes inflammation may cause further inflammation; it can become self-

perpetuating. More inflammation can created in response to the existing inflammation[1] .Gels are a relatively newer class of dosage form created by entrapment of large amounts of aqueous or hydroalcoholic liquid in a network of colloidal solid particles, which consist of inorganic substances, like aluminium salts or organic polymers of natural or synthetic origin [2].

They have a higher aqueous component that permits greater dissolution of drugs, and also allow easy migration of the drug through a vehicle that is necessarily a liquid, compared with the ointment or cream base. These are better in terms of use and patient acceptability. Within many advantages of gels a major limitation is in the delivery of hydrophobic drugs. So to reduce this limitation, emulgels are formulate and used so that even a hydrophobic therapeutic moiety can enjoy the unique properties of gels [3].

Diclofenac sodium, a phenylacetic acid derivative, a non-steroidal, anti-inflammatory, analgesic agent use in rheumatoid arthritis, degenerative disease of joints, ankylosing spondylitis and allied conditions, and in the pain treatment resulting from minor surgery, trauma and dysmenorrhoea. This drug has shown to be effective in treatment of rheumatic and non rheumatic conditions. Diclofenac has been considerd a NSAID since its introduction [4]. The liquid phase may either be polar or apolar in nature. If the liquid phase is polar nature, then the gels may be regarded as hydrogels else as organogels . The solid components are regarded as gelator. The organogelators may be categorized into two groups based on their capability to form hydrogen bonding. The organogelators examples which do not form hydrogen hydrogen bonding include anthracene, anthraquinone, steroid based molecules whereas the hydrogen bond forming organogelators include aminoacids, amide and urea moieties and carbohydrates[5].

Some of the organogelators (e.g. lecithin, span or tween) accommodate aqueous phase within itself to form fiber-like structures, which physically interacts each other, resulting in the formation of a networked structure [6]. The organogels developed by this mechanism are usually non-crystalline, non-glassy, thermo-reversible in nature [6]. The apolar phase may either be mineral oil, organic solvent or vegetable oil. The research on organogels for applications in pharmaceutical and cosmetic industry has gained a tremendous momentum [6,7,8]. This may be attributed to the easy production techniques and inherent stability of the organogels [9]. Due to their easy spreadability, the organogels are becoming a vehicle of choice for cosmetics products and transdermal delivery systems [10].

Advantages of organogels [11]

A. **Template vehicle:** Lecithin organogels provide opportunities for incorporation of wide range of substances with diverse physicochemical characters like, chemical nature, solubility, molecular weight and size etc.
B. **Process Benefits:** Self-assembled supramolecular arrangement of surfactant molecules makes the process very simple and easy to handle.
C. **Structural/ Physical Stability:** Structural integrity of oranogels is maintained for longer time periods.
D. Chemical Stability: organogels are moisture insensitive and being organic in character also resist microbial contamination.
E. **Topical Delivery Potential:** They enhance the skin penetration and transport of the molecules.
F. **Safety:** Use of biocompatible, non-immunogenic materials and biodegradable makes them safe for long-term applications.

2. Materials and Method

2.1. Materials:

Diclofenac was procured as a gift sample from Himedia, Mumbai India. Span 80, Tween 80 and Sunflower oil were purchased from Loba chemie, Mumbai, Himedia, Mumbai, Adani wilmer, India . All reagents used were of analytical reagent grade.

2.2. Preparation of organogels:

Span 80 and tween 80 were mixed thoroughly in the proportion of 1:2 ratios (w/w) to obtain the surfactant mixture (SM), which was used as gelator. Specified amount of the SM was added to the SO, keep on stirring on a magnetic stirrer. The above mixture (gelator solution, GS) was stirred for 20 min. Subsequently, water was poured drop-by-drop to the GS using a burette until there was a formation of organogel or the total fraction of water has reached 80% of the volume of the GS-water mixture. Depends on the composition of the GS-water mixture, the system either formed gelled structures or remained as liquid mixtures. A ternary plot depicting the ratio of SM, water and SO was prepared to figure out the compositions, which formed organogels. Samples for morphological studies were prepared in a similar manner using 0.01 % (w/v) aqueous rhodamine B solution as the polar phase. DF-loaded samples were prepared by dispersing DF into the SO, which was subsequently used for the development of organogels. The final concentration of DF in organogels was maintained at 1 % (w/w).

Table 1: Formulation

Ingredients	Formulation No.					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
Diclofenac (mg)	100	100	100	100	100	100
Span 80 (gm)	0.5	0.5	0.5	0.5	0.5	0.5
Tween 80 (gm)	0.5	0.5	0.5	0.5	0.5	0.5
Sunflower oil (gm)	1	2	3	4	5	6
Water (gm)	qs	qs	qs	qs	qs	qs

Optimization of formulation: Optimization was based upon the higher drug content and in vitro drug release.

Table 2: Optimized formulation

Ingredients	Formulation No.			
	OF1	**OF2**	**OF3**	**OF4**
Diclofenac (mg)	100	100	100	100
Span 80 (gm)	0.5	0.5	0.5	0.5
Tween 80 (gm)	0.5	1	1.5	2.0
Sunflower oil (gm)	4	4	4	4
Water (gm)	Qs	qs	qs	qs

3. Evaluation parameter:

3. 1 pH determination

pH of the formulation was determined by using digital pH meter. pH meter electrode was washed by distilled water and then dipped into formulation to measure pH and this process was repeated 3 times.

3.2 Measurement of viscosity

Viscosity of the formulation was measured by the Brookfield viscometer using spindle no. L63. Viscosity was measured at different rpm i.e 10, 20, 50, 100. Repeated the process 3 times.

3.3 Globule size determination

Globule size of the formulation was determined by optical microscopy using stage micrometer and eye piece. Initially calibrate the eye piece using stage micrometer and then measure the size of the globules present in the formulation. Globule size was also can be measured by zeta sizer.

3.4 Drug content study

Drug content study was done to determine the amount of the drug present in the certain quantity of the formulation. Took 1 gm of the formulation into 10 ml volumetric flask added 1 ml methanol in it and shake well and make up the volume with PBS pH 7.4. Now poured the mixer into centrifugation tube and centrifuged it at 5000 rpm for 30 min. After centrifugation filtered the mixer then measured absorbance by using spectrophotometer at 281.00 nm.

3.5 Drug release study

The release studies were carried out in franz diffusion cell containing PBS pH 7.4. PBS pH 7.4 was placed in a franz diffusion cell. The system was assembled on a magnetic stirrer and the medium was equilibrated at 37 ± 5^0C. Organogel formulation was filled in the system. The cellophane membrane containing the sample was suspended in the medium. Aliquots were withdrawn (1 ml) at specific intervals, filtered and the apparatus was replenished immediately with same quantity of fresh buffer medium. Took 1 ml solution and make up the volume upto 10 ml with PBS pH 7.4. Then measured absorbance by using spectrophotometer at 281.00 nm. The cumulative % drug release was calculated using standard calibration curve.

Details of dissolution testing:

- Dissolution apparatus: Franz diffusion apparatus
- Dissolution media: Phosphate buffer saline pH 7.4
- Speed: 100 rpm
- Aliquots taken at each time interval: 1 ml
- Temparature: 37 ± 2^0C
- Wavelenght: 281 nm

3. Results and Discussion

4.1 1 identification of drug

4. 1.1 Physical description: The drug was found white in color and odourless.

4. 1.2 Melting point: Melting point was found 282 °C

4. 1.3 FT-IR of Drug and polymer

Table 9: Interpretation of FT-IR spectra

Functional group	Reference peak	Obsereved peak of drug	Observed peak of span80	Observed peak of tween 80	Observed peak of drug and polymer mixture
C-H (methyl group)	2962-720	-	2921.96	2923.88	2923.88
C-H (methylene group)	3000-1300	2970.17	2921.96	--	2923.88
C-C	1600-1585	1573.81	-	-	1573.81
C-O (acid group)	1320-1210	1305.72	-	-	1305.72
C-Cl	850-550	842.83	-	-	844.76
C-N	1250-1020	1249.79	-	-	1249.79
C-O-C	1150-1085	-	1108.99	1108.99	1089.71
N-H	near3500	3585.42	-	-	3585.42
-OH	3700-1330	3585.42	-	-	3585.72
C=O (ester)	1750-1735	-	1735.81	1735.81	1731.96

4.1.3.1 Identification of drug and polymer

The drug and polymer are identified by FT-IR as the observed peak of drug and polymer was matched with reference peak of drug and polymer respectively.

4.1.3.2 Drug and polymer compatibility study

The compatibility between drug and polymer was determined by FT-IR. The position of peak in FT-IR spectra of pure drug and polymers were compared with those in FT-IR spectra of drug-polymer mixture. No disappearance or significant shift in the peak position of drug and polymer in the spectra was observed, which proves that the drug and polymers used for the study are compatible.

4.2 Solubility study

Table 10: Solubility of diclofenac

S. No	Solvent	Solubility (mg/ml)
1	Methanol	24.280
2	Ethanol	34.852
3	Water	51.2541
4	PBS pH 7.4	5.82520

The solubility study of diclofenac in different solvent suggests that the drug is maximum soluble in water and minimum soluble in PBS pH 7.4 than other solvent.

4. 3 Partition Coefficient

The partition coefficient of diclofenac between octanol and water was found to be 1.165.

4. 4 Calibration curve of diclofenac in different solvents

Calibration curve of diclofenac in methanol was prepared and R^2 value was found 0.980.

Calibration curve of diclofenac in pH 7.4 buffer was prepared and R^2 value was found 0.993.

4 .5 Evaluation parameters:

4. 5.1 pH determination:

pH determination of all the formulations was found in range of pH7.2- pH7.5. This results showed that formulation is in the range of the skin pH. Results was showed in the table:

Table 11: pH determination of formulations

Formulation	pH value
F1	7.3
F2	7.2
F3	7.4
F4	7.4
F5	7.5
F6	7.4

Table 12: pH determination of optimized formulation

Formulation	pH value
OF1	7.4
OF2	7.4
OF3	7.3
OF4	7.4

4. 5.2 Measurement of viscosity:

Viscosity was measured by brookfield viscometer and found 439-451 cps at 10 rpm, 200-220 cps at 20 rpm, 113-125 cps at 50 rpm and 24-30 cps at 100 rpm. Which was found optimum viscosity for gel formulation.

Table 13: Viscosity of formulations

Formulation no.	Viscosity (cps) at RPM			
	10	**20**	**50**	**100**
F1	442	200	113	25
F2	450	205	120	27
F3	439	201	125	24
F4	448	210	118	30
F5	445	213	120	28
F6	451	220	123	27

Viscosity of the formulation was found 441-451 cps at 10 rpm, 202-212 at 20 rpm, 114-122 cps at 50 rpm, 25-29 cps at 100 rpm, which was found optimum viscosity for the formulation.

Table 14: Viscosity of optimized formulations

Formulation No.	Viscosity (cps) at RPM			
	10	**20**	**50**	**100**
OF1	443	203	114	26
OF2	448	202	119	25
OF3	441	204	122	28
OF4	451	212	121	29

4..5.3 Globule size determination: Globule size of the formulation was determined by optical microscopy and was found in the size range of 88.60 ± 4.15 µm to 110.30 ± 9.77 µm.

Table 15: Globule size of formulation

Formulation No.	Globule size (µm)
F1	106.50 ± 8.47
F2	98.90 ± 11.29
F3	110.30 ± 9.77
F4	92.90 ± 7.17
F5	99.80 ± 7.55
F6	88.00 ± 4.15

Globule size of the optimized formulation was determined by optical microscopy and was found in the size range of 92.90 ± 9.37 µm to 104.30 ± 8.67 µm.

Table 20: Globule size of optimized formulation

Formulation No.	Globule size (µm)
OF1	96.50 ± 9.54
OF2	98.90 ± 12.33
OF3	104.30 ± 8.67
OF4	92.90 ± 9.37

4. 5.4 Drug content study:

Drug content study of formulations was shown in the table. The study shows that formulation no. F4 gave the best results instead of the other formulations. So further study of the formulation would be performed with 4 gm sunflower oil.

Table 17: Drug content study of formulation

Formulation No.	% Drug content
F1	63.60 %
F2	66.07 %
F3	69.78 %
F4	77.61 %
F5	74.86 %
F6	70.12 %

Drug content study of optimized formulation was shown in the table. As per the results formulation OF2 have highest drug content and gave the best results. All four formulations was selected for the drug release study.

Table 22: Drug content study of optimized formulation

Formulation No.	% Drug content
OF1	76.60 %
OF2	87.07 %
OF3	79.58 %
OF4	75.66 %

4. 5.5 Drug release study: Drug release study of the formulation was shown in the table. Drug release study was performed on the all formulations. In this result formulation no. F4 showed better results so was selected for further study.

Table 19: Drug release study of formulation

Time	% Cumulative drug release					
	F1	F2	F3	F4	F5	F6
30 min	7.67	11.38	10.47	10.66	9.86	11.66
1 hr.	14.25	16.04	19.14	23.46	18.78	16.25
2 hrs.	25.34	28.81	31.18	35.16	31.80	30.04
3 hrs.	39.45	40.29	44.39	50.67	49.51	44.72
4 hrs.	50.65	52.28	53.27	59.88	57.87	53.14
5 hrs.	57.89	61.52	62.38	65.41	66.81	60.82
6 hrs.	--	--	--	72.58	--	--

Drug release study of the optimized formulations was shown in the table. This study was performed on the all batches. Results showed that drug was released in 6 hours and OF2 gave the best result.

Table 20: Drug release study of optimized formulation

Time	% Cumulative drug release			
	OF1	OF2	OF3	OF4
30 min	11.57	13.86	9.76	8.95
1 hr.	19.05	23.47	21.56	17.38
2 hr.	37.63	39.88	36.97	34.82
3 hrs.	46.31	52.79	48.56	44.69
4 hrs.	53.88	63.28	56.12	50.92
5 hrs.	64.01	72.53	69.12	61.41
6 hrs.	72.09	83.34	77.95	69.84

Release Kinetics: The results obtained from *in vitro* drug release studies were plotted adopting five different mathematical models of data treatment as follows:

Table 21: Release kinetics data of OF2

Time (Hrs)	Log T	SQRT	%CDR	Log %CDR	Log % drug retained	(% drug retained)$^{1/3}$
0.5	-0.301	0.707	13.86	1.141	1.935	4.416
1	0	1	23.47	1.370	1.883	4.245
2	0.301	1.414	39.88	1.600	1.779	3.917
3	0.477	1.732	52.79	1.722	1.674	3.614
4	0.602	2	63.28	1.801	1.564	3.323
5	0.698	2.236	72.53	1.860	1.438	3.017
6	0.778	2.449	83.34	1.920	1.221	2.554

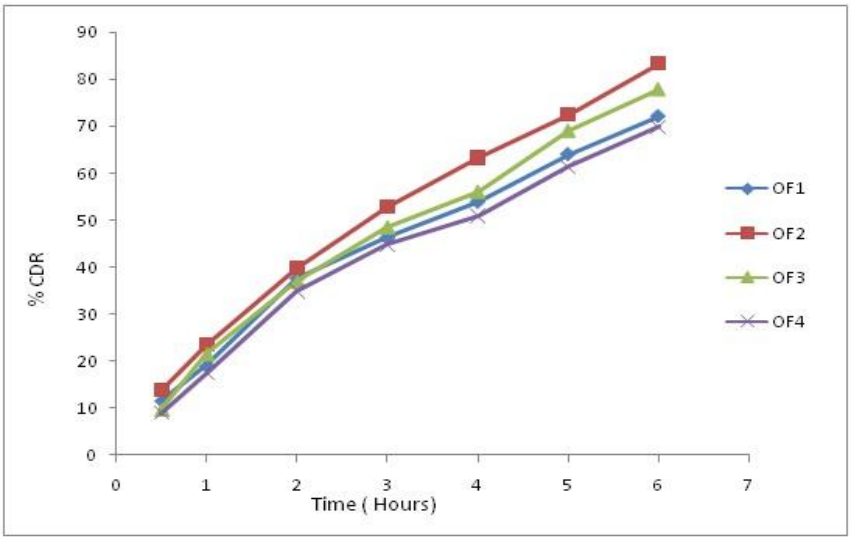

Figure 10: Drug release curve of optimized formulations

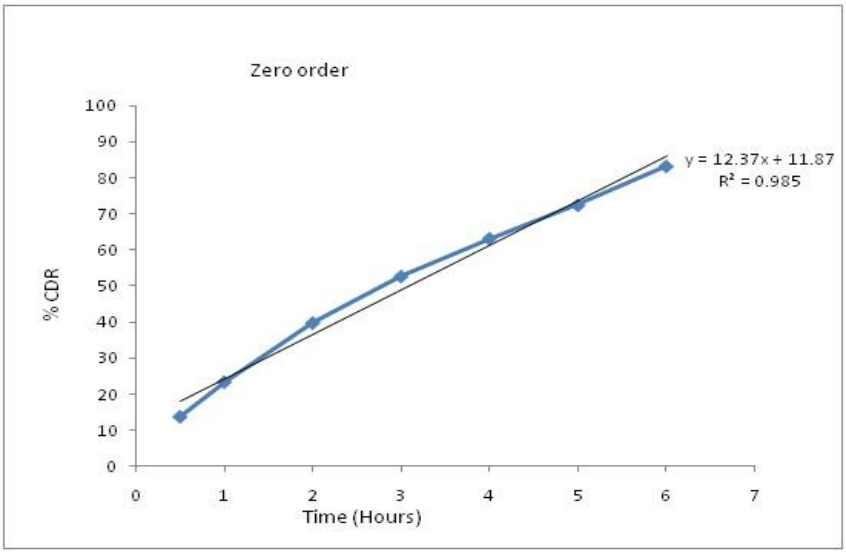

Figure 11: % Cum. Drug Release Vs. Time (Zero order rate kinetics)

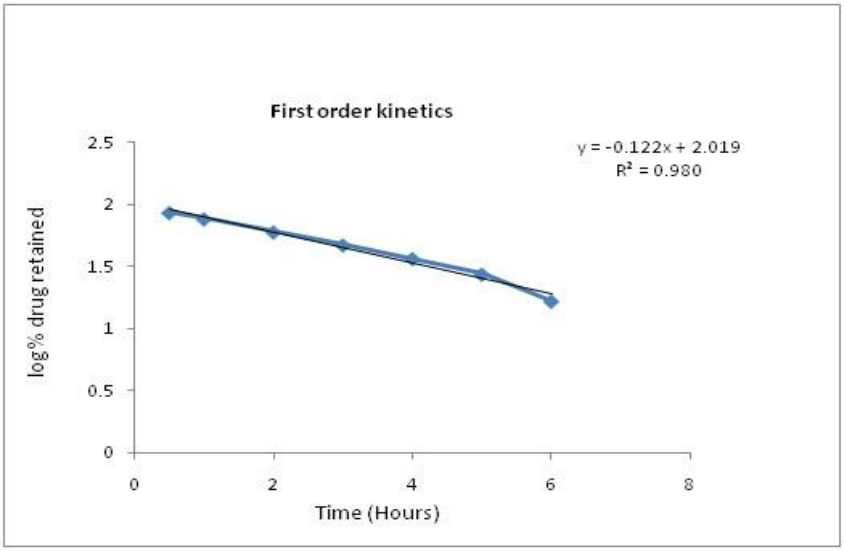

Figure 12: Log % Cum. Drug Retained Vs. Time (First order rate kinetics)

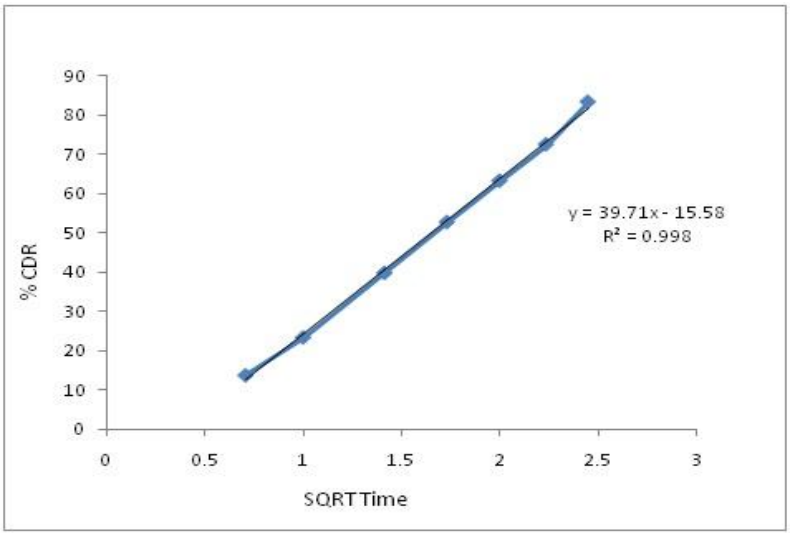

Figure 13: % Cum. Drug release vs SQRT (root time). (Higuchi model)

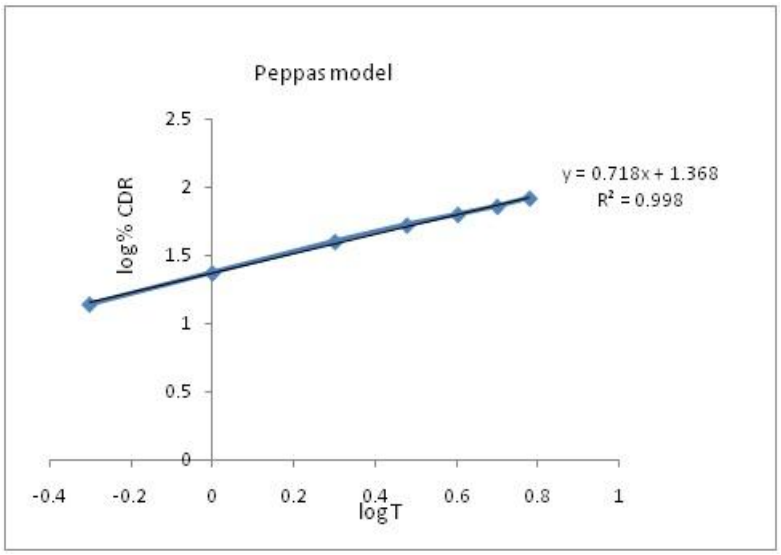

Figure 14: Log % Cum. Drug Release Vs. Log Time (Peppas exponential equation)

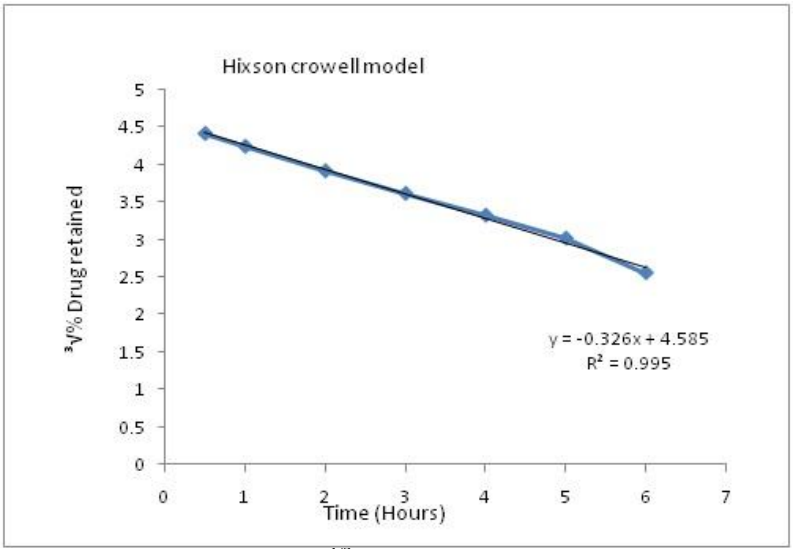

Figure 15: (% Cum. Drug Retained)$^{1/3}$ Vs. Time (Hixon-Crowell's erosion equation)

The curve fitting results of the release rate profile of the designed formulation are shown in the Figures 24-28 which gave an idea on the release rate and the mechanism of release. The values were compared with each other for model and drug equation based on the highest regression values (r), fitting of the release rate data to the various models revealed that the formulation OF2 was best fitted with peppas exponential equation. The Peppas model is widely used when the release mechanism is not well known or when more than one type of release phenomenon could be involved. 'n' value could be used to characterize different release mechanisms.

Peppas model equation is given as:

$\% R = K t^n$

Or $\text{Log } \% R = \log K + \log t$

Where R = drug release, k =constant, n= slope, t=time.

'n'	**Mechanism**
< 0.5	Fickian Diffusion (Higuchi matrix)
0.5 < n < 1	Non Fickian Diffusion or anomalous release
> 1	Case II Transport

In the case of the Fickian release mechanism, the rate of drug release is much less than that of polymer relaxation (erosion). So the drug release is chiefly dependent on the diffusion through the matrix. In the non-Fickian (anomalous) case, the drug release rate is due to the combined effect of drug diffusion and polymer relaxation. Case II release usually refers to the polymer relaxation. The n values for formulation OF2 was found 1.368, indicating that the release mechanism was case II transport (> 1). Based on the n value OF2, drug release from formulation was controlled by polymer relaxation (erosion).

4. Conclusion

Diclofenac is one of the most potent and successful non-steroidal anti-inflammatory agents. We have introduced special drug carriers, so-called organogel for the non-invasive delivery of pharmaceuticals across the skin. These drug carriers trespass the intact skin spontaneously, probably under the influence surfactant. The physicochemical properties of the drug and formulation were analyzed by ultraviolet spectrometry (UV), infrered spectrometry (IR), and solubility. Different necessary evaluation were performed on the formulations like pH measurement, viscosity measurement, globule size determination, drug content study and drug release study. On the basis of results of the evaluation study formulation was optimized and studied further.

In this study, we found all the formulations were in pH range of 7.3-7.5 which is similar to the skin pH and can be topically administered easily. OF2 was found pH 7.4. Viscosity of the formulation was found in the optimum range for the gel preparation. Viscosity of OF2 was found 448 cps at 10 rpm, 202 cps at 20 rpm, 119 cps at 50 rpm, 25 cps at 100 rpm. Globule size was found in 88.00 µm- 110.30 µm size range. Globule size of OF2 was found 98.8 ± 12.33 µm. Formulation was optimized on the basis of drug content study and drug release study and was found that formulation containing 4 gm sunflower oil and having ratio of span 80 and tween 80 1:2 gave the best results. Formulation OF2 was found optimized and ideal formulation exhibited 87.07% drug content and 83.34% drug release. Release kinetics of the formulation indicated that the release mechanism was case II transport and was controlled by polymer relaxation (erosion). From the present study, it can be concluded that the prepared OF2 organogel provided the ideal drug content and drug release.

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