RESEARCH ARTICLE

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Design and Release Kinetic Studies of Nimesulide Bioadhesive Topical Gel

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Abstract: The objective of the present investigation was to develop topical gel of nimesulide using model polymers such as hydroxypropyl methylcellulose K100M (HPMC K100M) and carbopol 940 at different concentrations individually and in combination. The drug and polymers compatibility study was carried out by FTIR technique. The gels were evaluated for drug content, viscosity, pH, homogenecity, spreadability and *in-vitro* drug release. The FTIR spectra of drug alone and in physical mixture with polymers did not show any shift in major peaks, which indicates no drug-polymer interaction. All the data obtained from above physicochemical parameters were satisfactory. *In-vitro* drug release of gels was performed using Franz diffusion cell with cellulose acetate membrane in phosphate buffer pH 7.4 as receptor medium. According to the release study, the drug release was decreasing with the increasing polymer concentration in each formulation. The correlation coefficient (R^2) values demonstrate that the drug release pattern followed Higuchi model except BTG2 and BTG4. The release exponent (n) values were within 0.78 to 0.98 for all formulations. The above results showed that swelling and diffusion (Non-Fickian diffusion) were the drug release mechanism.

INTRODUCTION

Gels are transparent or translucent semisolid formulations containing a high ratio of solvent/gelling agent.

Nimesulide is a second generation non-steroidal anti-inflammatory drug, which is widely used in the long term therapy of rheumatoid arthritis, in alleviating pain and inflammation. Its biological half-life have been reported to be 3 to 4 hours, requires multiple daily dosing for maintaining therapeutic effect throughout the day which means more fluctuation. But bioadhesive topical gels (BTGs) avoid this drawback by increasing the contact between the formulation and biological membrane, so as to avoid the fluctuation of formulation and act as a sustained release formulation. [1]

Topical application of the drug prevents these side effects and offers potential advantage of delivering the drug at the site of action. Most importantly controlled release of drug from these BTGs avoids the more fluctuation, reduces the cost of the therapy and improves the patient compliance. [2]

In this study, nimesulide topical gels were formulated using natural bioadhesive polymers and were evaluated with different *in-vitro* evaluation studies.

MATERIALS AND METHODS

The drug, Nimesulide was purchased from Yarrow Chemical Products, Mumbai. Carbopol 940, HPMC K100M, Methyl Paraben were purchased from Yarrow Chemical Products Mumbai. Triethanolamine was purchased from Burgoyne Burtidges and Co., Mumbai. Glycerol was purchased from Rankem, RFCL Ltd., New Delhi.

Calibration Curve of Nimesulide

Solutions of nimesulide (2, 4, 6, 8, 10 µg/ml) was prepared using phosphate buffer pH 7.4 and absorbance was measured using UV-Visible spectrophotometer (Shimadzu 1700, Japan) at 392 nm (Figure 1).

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Preparation of Nimesulide Bioadhesive Topical Gel [3, 4]

Gels were prepared by cold mechanical method. Required quantity of polymer (Carbopol) was weighed and it was sprinkled slowly on surface of purified water for 2 hrs. After the polymer was completely dissolved, 3 to 5 drops of Triethanolamine was added (quantity necessary to obtain gel) to neutralize the gel and it maintains the pH of the gel.

Mixture of Methyl Paraben (as a preservative), Nimesulide and Glycerol (which behaves as the penetration enhancer) was prepared in another beaker with sufficient quantity of water. This mixture was added to the prepared gel with stirring till the mixture gets dispersed completely.

Three formulations of bioadhesive topical gels were prepared by using Carbopol 940 in different proportion and another three formulations were prepared by using Carbopol 940 and HPMC K100M. The prepared gel were packed in wide mouth glass jar covered with screw capped plastic lid after covering the mouth with an aluminum foil and were kept in dark and cool place.

Evaluation of Nimesulide Bioadhesive Topical Gel

1. Clarity [4, 5]

The clarity of various formulations was determined by visual inspection under black and white background and it was graded as follows; clear: + and very clear (glassy): ++.

2. pH Measurement [4, 5]

10% of gel solution was prepared in distilled water (2.5 g of gel in 25 ml of distilled water). Then the pH was measured using pH-meter.

3. Homogeneity [4, 5]

All developed gels were tested for homogeneity by visual inspection after the gels have been set in the container for their appearance and presence of any aggregate.

4. Spreadability Study [4-8]

It was determined by wooden block and glass slide model developed in the laboratory. For the determination of the spreadability 1 g of gel was sandwiched between two glass slides and compressed to a uniform thickness and remove entrapped air by placing 500 g weight for 5 minutes. Then

Table 1: Formulation Design for the Preparation of Topical Gel

Ingredients	BTG1	BTG2	BTG3	BTG4	BTG5	BTG6
Nimesulide (mg)	100	100	100	100	100	100
Carbopol 940 (mg)	500	1000	1500	500	1000	1500
HPMC K100M (mg)	-	-	-	100	100	100
Triethanolamine (ml)	0.23	0.23	0.23	0.23	0.23	0.23
Glycerol (ml)	2.20	2.20	2.20	2.20	2.20	2.20
Methyl Paraben (mg)	15.00	15.00	15.00	15.00	15.00	15.00
Distilled Water (ml) upto	100	100	100	100	100	100

Table 2: Evaluation Parameters of Nimesulide Bioadhesive Topical Gel

Formulations Code	Clarity*	pH	Homogeneity	Spreadability (g.cm/sec)	Drug Content
BTG1	+ +	6	Good	21.73	95.20
BTG2	+ +	6.5	Good	20.13	92.38
BTG3	+ +	7	Good	15.33	102.12
BTG4	+	7.5	Good	31.66	104.18
BTG5	+	6.5	Good	22.12	97.27
BTG6	+	6	Good	35.15	100.00

*clear: + and very clear (glassy): ++

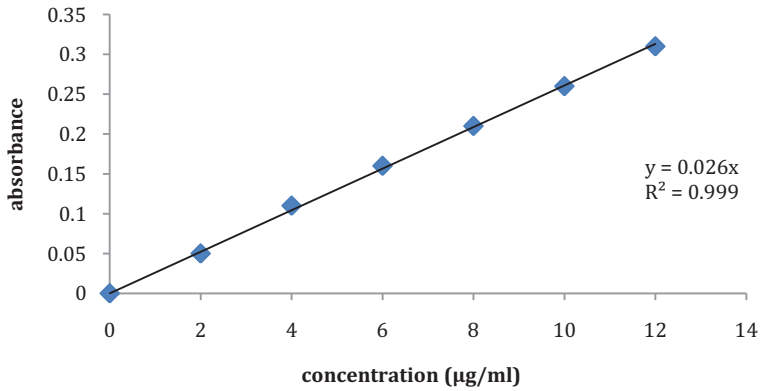

Figure 1: Standard curve of nimesulide in phosphate buffer pH 7.4 at 392 nm

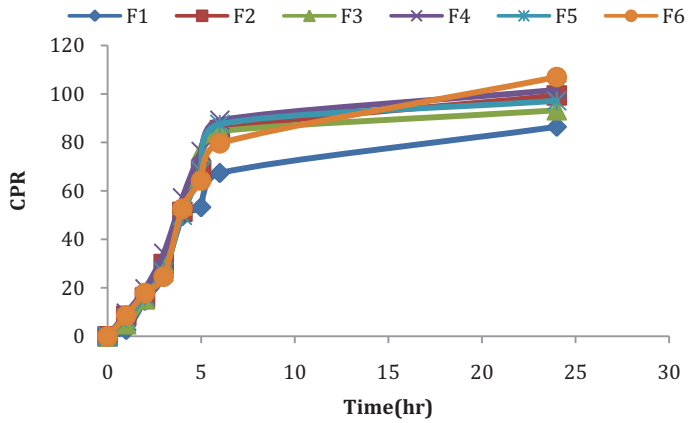

Figure 2: Dissolution profile of nimesulide bioadhesive topical gel formulations

the excessive gel was removed with filter paper carefully without disturbing the sealed slides. Weight of total 80 g was placed on one side of the model and the time required to separate the two slides was noted.

Spreadability was calculated by using the following formula:

$$S = \frac{M \times L}{T}$$

Where, S is the spreadability, M is the weight tied to one slide (80 g in our case), L is the length/distance moved on the glass slide, T is the time taken to separate the slide completely from each other.

5. Drug Content [5]

Drug content of gel was determined by dissolving accurately weighed 1g of gels in phosphate buffer pH 7.4. After suitable dilution absorbance was recorded by using

Table 3: Weight Gain by Nimesulide Bioadhesive Topical Gel

Batch No.	Time (min)								
	0	15	30	45	60	75	90	105	120
BTG1	1.182	1.272	1.351	1.420	1.525	1.615	1.640	1.679	1.712
BTG2	1.289	1.498	1.651	1.816	1.849	1.899	1.943	1.956	1.975
BTG3	1.171	1.236	1.338	1.368	1.400	1.469	1.568	1.625	1.653
BTG4	1.228	1.589	1.629	1.695	1.729	1.779	1.820	1.855	1.879
BTG5	1.250	1.332	1.468	1.655	1.779	1.835	1.889	1.935	1.960
BTG6	1.325	1.536	1.635	1.678	1.740	1.850	1.940	1.989	1.998

Table 4: % Swelling Index of Nimesulide Bioadhesive Topical Gel

Batch No.	Time (min)							
	15	30	45	60	75	90	105	120
BTG1	9.65	16.26	20.65	29.70	38.58	40.50	44.23	46.72
BTG2	18.18	30.50	43.86	45.59	49.55	52.89	53.90	55.78
BTG3	4.25	16.55	41.90	44.59	49.58	52.84	53.88	56.80
BTG4	30.10	34.80	38.62	42.44	46.40	49.85	52.75	54.60
BTG5	8.46	19.30	32.35	41.90	48.63	51.70	55.70	57.48
BTG6	18.84	26.20	27.00	31.79	42.68	47.85	51.50	52.85

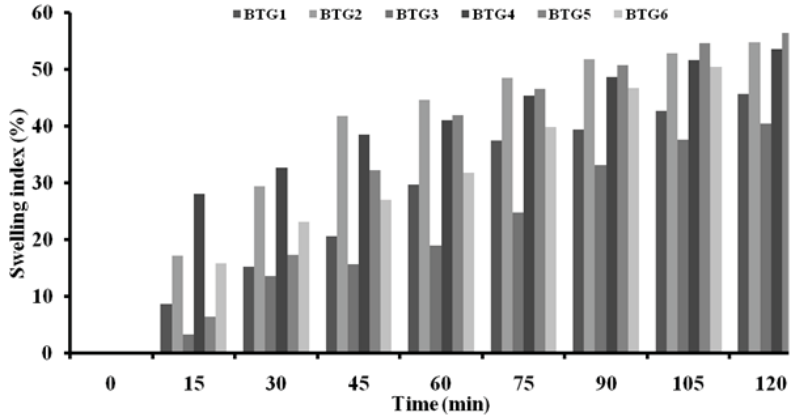

Figure 3: Graph for % swelling index of nimesulide bioadhesive topical gel formulations

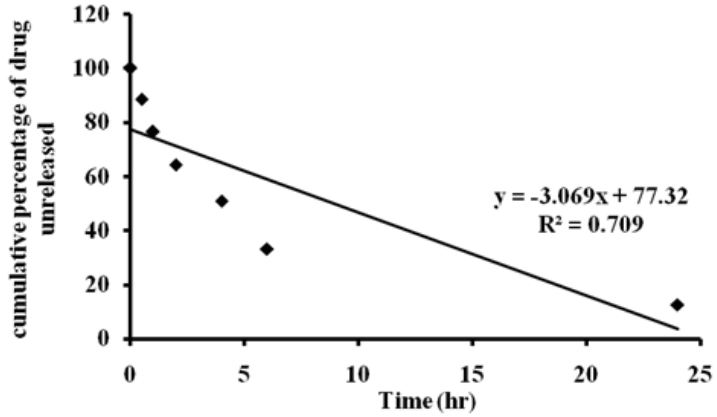

Figure 4: *In-vitro* release of nimesulide from BTG3 in phosphate buffer pH 7.4, zero order release

UV-visible spectrophotometer at 392 nm. Drug content was determined using slope of standard curve.

6. *In-Vitro* Drug Diffusion Study [5]

Cellophane membrane was used for this study. In Franz diffusion cell, 1.0 g of gel was kept in donor compartment. The entire surface of membrane was in contact with the receptor compartment containing phosphate buffer pH 7.4. The study was carried out for 24 hrs with the interval of 0.5, 1, 2, 4, 6, 24 hrs at room temperature. 0.5 ml sample was withdrawn from the donor compartment at predetermined period of time and same volume was replaced with fresh phosphate buffer pH 7.4. The absorbance of withdrawn sample was measured at 392 nm to estimate concentrations of nimesulide.

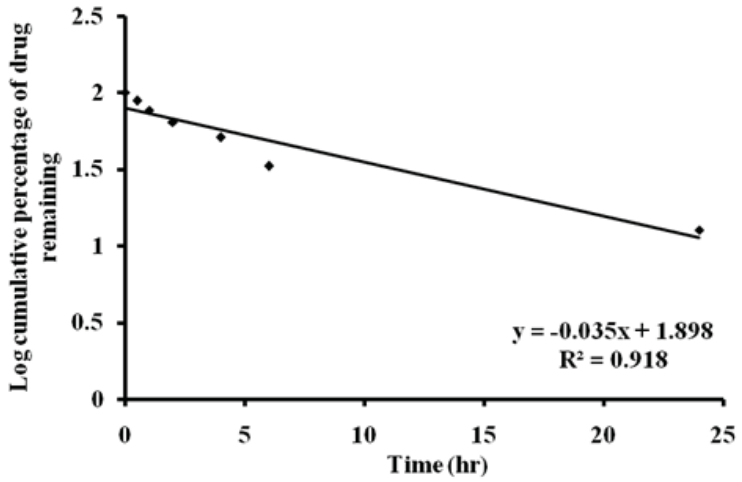

Figure 5: *In-vitro* release of nimesulide from BTG3 in phosphate buffer pH 7.4, first order release

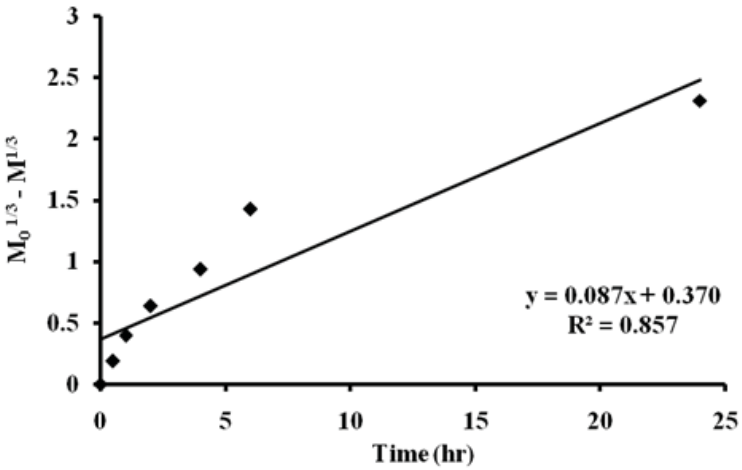

Figure 6: *In-vitro* release of nimesulide from BTG3 in phosphate buffer pH 7.4, Hixon-Crowell cube root laws

Table 5: Comparison of Orders of *In-Vitro* Release of Nimesulide from BTG1 to BTG6

Formulation Code	*In-Vitro* Release of Nimesulide in Phosphate Buffer pH 7.4 Regression Equations	
	Zero Order	First Order
BTG1	y = -3.442x + 79.48 R^2 = 0.713	y = -0.046x + 1.924 R^2 = 0.952
BTG2	y = -3.705x + 77.60 R^2 = 0.695	y = -0.115x + 2.035 R^2 = 0.999
BTG3	y = -3.069x + 77.32 R^2 = 0.709	y = -0.035x + 1.898 R^2 = 0.918
BTG4	y = -3.836x + 76.35 R^2 = 0.713	y = -0.083x + 1.956 R^2 = 0.989
BTG5	y = -3.307x + 74.45 R^2 = 0.668	y = -0.049x + 1.892 R^2 = 0.940
BTG6	y = -3.017x + 81.52 R^2 = 0.716	y = -0.029x + 1.917 R^2 = 0.894

7. Effect of Swelling Index Study on Drug Release from BTGs [9, 10]

Swelling of the polymer depends on the concentration of the polymer, ionic strength and the presence of water. To determine the swelling index of prepared topical gel, 1 g of gel was taken in cellophane paper bag and then placed separately in a 50 ml beaker containing 10 ml phosphate buffer pH 7.4. Then bag were removed from beakers at different time intervals and put it on dry place for some time after it reweighed. Swelling index was calculated as follows:

$$\text{Swelling Index (SW)}\ \% = \frac{\text{Wt} - \text{Wo}}{\text{Wo}} \times 100$$

Where, (SW) % = equilibrium percent swelling, Wt = weight of swollen gel after time t and Wo = original weight of gel at zero time.

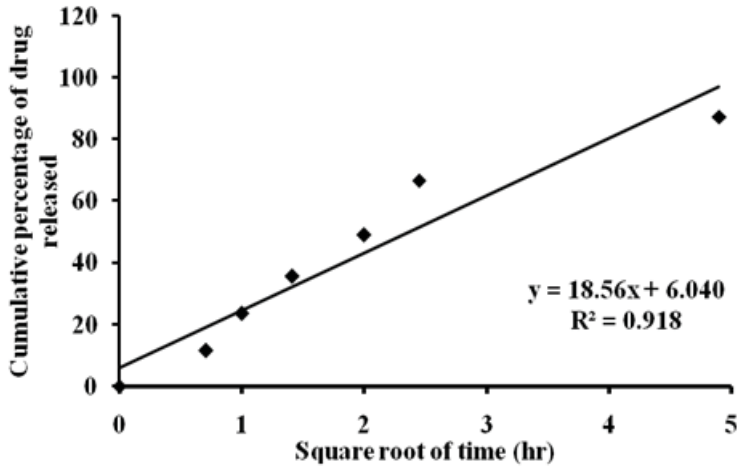

Figure 7: *In-vitro* release of nimesulide from BTG3 in phosphate buffer pH 7.4, Higuchi's Model

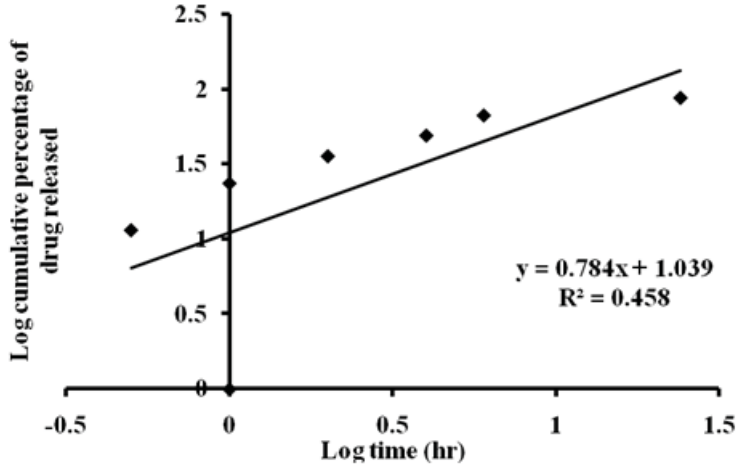

Figure 8: *In-vitro* release of nimesulide from BTG3 in phosphate buffer pH 7.4, korsmeyer-peppas model

8. Release Kinetics and Mechanisms [11, 12]

Data obtained from dissolution studies were fitted to various kinetic equations. The kinetic models used were zero order (cumulative percentage of drug unreleased vs. time in min), first order (log cumulative percentage of drug remaining vs. time), Hixson-Crowell model ($M_0^{1/3} - M^{1/3}$ vs. time in min), Higuchi's model (cumulative percentage of drug released vs. square root of time) and Korsmeyer – Peppas model (log cumulative percentage of drug released vs. log time) equation. The data were used to find out R^2 value. The results of release kinetics are given in Table 6 and Figure 4-8.

RESULTS AND DISCUSSION

Clarity

Carbopol 940 gels (formulations BTG1 – BTG3) were found to be sparkling and transparent. While the gels with HPMC and Carbopol 940 (formulations BTG4 – BTG6) was found to be translucent. All formulations were free from the presence of the particles (shown in Table 2).

pH

The pH value of developed BTG1 – BTG3 formulations were in range 6.78 to 7.01 and that of BTG4 – BTG6 was in the range of 6.72 to 7.04 (Table 2).

Homogenecity

All developed formulations were having good homogenecity with absence of lumps. The developed preparations were much clear and transparent (Table 2).

Spreadability

The value of spreadability indicates that gel is easily spreadable by small amount of shear. Spreadability of HPMC and Carbopol gel was in the range of 19.15 – 28.13 g.cm/sec. While that of the Carbopol alone was found in the range of 13.33 – 18.37 g.cm/sec. Hence, it can be conferred that the spreadability of the formulations prepared with HPMC and Carbopol was better than the Carbopol. The reason for this might be the increase in the hydrophilicity and the internal texture of the formulations due to the HPMC. Spreadability of the combination formulation was good as compared to the Carbopol gel (Table 2).

Drug Content

The percentage drug content of all formulations was found to be in range of 95.83 – 108.33%. The percentage drug content of all prepared gel formulations were found satisfactory. Hence method adopted for preparation was found suitable (Table 2).

Table 6: Regression Equations of *In-Vitro* Release of Nimesulide from BTG1 to BTG6

Formulation Code	*In-Vitro* Release of Nimesulide in Phosphate Buffer pH 7.4		
	Hixon-Crowell Model	Higuchi's Model	Korsmeyer Peppas Model
BTG1	y = 0.108x + 0.315 R^2 = 0.887	y = 20.65x + 2.161 R^2 = 0.908	y = 0.957x + 0.911 R^2 = 0.594
BTG2	y = 0.165x + 0.269 R^2 = 0.954	y = 22.35x + 2.416 R^2 = 0.895	y = 0.981x + 0.925 R^2 = 0.595
BTG3	y = 0.087x + 0.370 R^2 = 0.857	y = 18.56x + 6.040 R^2 = 0.918	y = 0.784x + 1.039 R^2 = 0.458
BTG4	y = 0.259x + 0.114 R^2 = 0.996	y = 23.04x + 3.153 R^2 = 0.910	y = 0.906x + 0.999 R^2 = 0.540
BTG5	y = 0.109x + 0.418 R^2 = 0.862	y = 20.30x + 7.083 R^2 = 0.891	y = 0.819x + 1.054 R^2 = 0.468
BTG6	y = 0.078x + 0.300 R^2 = 0.840	y = 18.11x + 2.374 R^2 = 0.912	y = 0.905x + 0.902 R^2 = 0.581

Table 7: Slope of Korsmeyer-Peppas Equation and Proposed Release Mechanisms

Slope (n)	Mechanism
<0.5	Fickian diffusion (Higuchi Matrix)
0.5 < n < 1	Non-Fickian diffusion
1	Case II transport

Release Kinetics

The release data of nimesulide from all the formulations were given in Figure 2. A perusal to Figure 2 indicated that the drug release was sustained in Carbopol (BTG3) and HPMC-Carbopol combinations (BTG6). Data of the *in-vitro* release were fit into different equations and kinetic models to explain the release kinetics of nimesulide from these gel formulations. The release kinetics of nimesulide followed first order from all the formulations BTG1 to BTG6. The better fit (highest R^2 values) was observed in case of Higuchi's model than Hixon–Crowel model except BTG2 and BTG4. Hence mechanism of drug release from the Nimesulide formulations BTG1, BTG3, BTG5 and BTG6 are diffusion controlled and drug release from BTG2 and BTG4 followed dissolution controlled.

Application of Hixon – Crowell cube root law, the equation $(M_0^{1/3} - M^{1/3}) = kt$, provides information about the release mechanism, namely dissolution rate limited. Application of Higuchi's equation ($M = K\ t^{1/2}$) provides information about the release mechanism, namely diffusion rate limited. Korsmeyer-Peppas model indicates that release mechanism is not well known or more than one type of release phenomena could be involved. The 'n' value could be used to characterize different release mechanisms.

The data of average values were processed as per Hixon-Crowell cube root law and are given in the Figure 6. The data of average values were processed as per Higuchi's equation and are represented in the Figure 7. The data of average values were processed as per Korsmeyer-Peppas model and are represented in the Figure 8. The linearity of data for all the models was identified from the Figures. The equations were generated through statistical procedures and reported in the Table 6.

According to Korsmeyer-Peppas model, a value of slope between 0.5 and 1 indicates an anomalous behavior (Non-Fickian). So, it indicates that release mechanism from all the formulations follows non-Fickian diffusion (anomalous behavior).

CONCLUSION

It can be concluded from the present study that proper selection of polymer and drug is a prerequisite for designing and developing a Bioadhesive topical gel. Taking the Carbopol alone and in combination of HPMC was found to affect the gel parameters like drug release, spreadability and swelling index.

Gel prepared with Carbopol 940 and combination of Carbopol 940 and HPMC K100M showed good homogeneity and clarity. However, the formulation BTG3 of Carbopol alone and BTG6 from the combination was selected as it showed better drug content, sustained release pattern, spreadability and swelling property.

REFERENCES

1. Jawahar N, Jayaprakash S, Maria Gerald Rajan N S, Nagarajan M, Dhachina Moorthi D, Jubie S, Manivannan R. Design and evaluation of sustained release suppositories of Nimesulide. Indian J Pharm Sci, 67(5):558-561, 2005.
2. Derle D V, Sagar B S H, Pimpale R. Microemulsion as a vehicle for transdermal permeation of nimesulide. Indian J Pharma Sci, 68(5):622-625, 2006.
3. Saleem M A, Sanaullah S, Faizan S. Formulation and evaluation of gatifloxacin topical gel. The Indian Pharmacist, 88-92, 2006.
4. Gupta G D, Gaud R S. Release rate of nimesulide from different gellants. Indian J Pharm Sci, 61:227-230, 1999.
5. Sanjay, Jain B D, Padsalg A, Patel K, Mokale V. Formulation, development and evaluation of fluconazole gel in various polymer bases. Asi J Pharm, 1:63-68, 2007.
6. Gupta G D, Gaud R S, Release rate of tenoxicam from acrypol gels. The Indian Pharmacist, 69-76, 2005.
7. Mutimer M N, Riffkin C, Hill J A, Glickman M E, Cyr G N. Modern ointment bases technology – II – Comparative evaluation of bases. J Am Pharm Assoc, XLV: 212-218, 1956.
8. Chakole C M, Shende M A, Khadatkar S N. Formulation and development of novel combined halobetasol propionate and

fusidic acid ointment. Int J Chem Tech Res, 1:103 – 116, 2009.
9. Kamel A E, Sokar M, Naggar V, Gamal S A. Chitosan and sodium alginate-based bioadhesive vaginal tablets. AAPS PharmSci, 4:1 – 7, 2002.
10. Mishra D N, Gilhotra R M. Design and characterization of bioadhesive *in – situ* gelling ocular insert of gatifloxacin sesquihydrate. DARU, 16:1 – 8, 2008.
11. Hadjioannou T P, Christain G D, Koupparis M A. Quantitative calculations in pharmaceutical practice and research. VCH Publishers Inc., New York, 345-8, 1993.
12. Bourne D W, Pharmacokinetics, In: Banker G S, Rhoides C T. Modern Pharmaceutics. Marcel Dekker Inc., NY, 4:67-92, 2002.

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