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FORMULATION AND EVALUATION OF IN-SITU GELLING MUCOADHESIVE LIQUID SUPPOSITORY OF NIMESULIDE

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ABSTRACT

The objective of the present study was to develop and evaluate in situ-gelling mucoadhesive liquid suppositories which are liquid at room temperature but forms a gel at body temperature. Liquid suppository of nimesulide, which is a non-steroidal anti-inflammatory drug (NSAID), was developed for use in rheumatic disease and other musculoskeletal disorders in order to improve patient compliance and systemic absorption. The thermo-sensitive mucoadhesive liquid suppositories were prepared by a cold method using poloxamers P407 and P188 (temperature sensitive gelation property), hydroxyl propyl methyl cellulose (HPMC) and Carbopol 934P. These polymers modulate the gel strength and impart mucoadhesive force to suppository bases. The characterization was carried on the basis of gelation temperature, gel strength, mucoadhesive force, and in-vitro release studies. Results showed from in-vitro release studies, that as the concentration of mucoadhesive polymer increases, release rate of the drug was decreased. So, it is concluded that gelation temperaturereduced upon addition of mucoadhesive polymer in the poloxamer solution which leads to increase the gel strength and mucoadhesive force.

KEYWORDS: In situ-gelling, NSAIDs, Mucoadhesive, *In-vitro* release studies, Rheumatic disease.

INTRODUCTION

Suppositories in latin term means "to place under". These are medicated solid dosage form inserted into the body orifice must deliver both systemic and local-acting medications.[1] In the past few years, increasing number of in situ gelling systems had been examined and patients had recorded their use in various biomedical applications, including drug delivery. This interest has been sparked by the potential advantages shown by in situ forming polymeric delivery systems such as simple manufacturing process, ease of administration, reduced frequency of dosage administration, improved patient compliance and comfort, compared to conventional dosage form.[2]

An attempt was made to develop a liquid rectal dosage form which transform into gel at body temperature, has suitable gel strength, does not leak out of the annus after administration and most important must possess suitable mucoadhesive force so as not reach at the end of colon.[3]

Liquid suppositories are developed to provide local effect, enhance drug absorption and avoid the first pass metabolism. These are mainly composed of poloxamers and mucoadhesive polymers. Mucoadhesive ploymers adhere to the rectal tissue without leakage after the dose. Poloxamer solutions are known to exhibit the phenomenon of reverse thermal gelation, remaining as solutions at low temperature and gelling upon increasing the temperature. Since they can be administered as liquids, it would be more acceptable to patients and cause less irritation to rectal mucosa compared to conventional suppositories. Polaxamer 407 and polaxamer 188 are bases for liquid suppositories. Poloxamer 188 is also used as solubility enhancer and in the liquid suppository formulations it is used to modify the gelation temperature. Poloxamers are known to have better mucoadhesive force, low toxicity, good drug release characteristics and compatibility with other chemicals.[4,5]

The rectal dosage forms are not common because of cultural and psychological bases there are several advantages to administration by rectal route. In cases of nausea and vomiting act taking medication orally may induce emesis so that drug is vomited before it absorbed. Irritation to the stomach and small intestine associated with certain drugs can be avoided. Hepatic first pass elimination of high clearance drug may be avoided partially. Its contact with digestive fluid is avoided, thereby preventing acidic and enzymatic degradation of some drug. Rectal suppositories are primarily intended for the treatment of constipation and haemorrhoids.[6,7]

Nimesulide (4-nitro-2-phenoxymethanesulfoanilide) is a selective COX-2 non-steroidal anti- inflammatory drug.

It is a relatively weak inhibitor of PG synthesis and there is some evidence to indicate relative COX-2 selectivity. Anti-inflammatory action may be exerted by other mechanisms as well, e.g. reduced generation of superoxide by neutrophils, inhibition of platelet active factor synthesis and tumour necrosis factor α release, free radical scavenging, inhibition of metalloproteinase activity in cartilage. Nimesulide has been used primarily for short-lasting painful inflammatory conditions like sports injuries, sinusitis, and other ear- nose-throat disorders, dental surgery, bursitis, low backache, dysmenorrhoea, postoperative pain, osteoarthritis and fever. Nimesulide has some side effects when taken orally i.e., heart burn, nausea, loose motions, headache, dizziness and kidney failure[8] The aim of this present research work was to develop a mucoadhesive and thermogelling system intended for improving the rectal administration of nimesulide, thus improves the bioavailability, and decreases the side effects as the absorbed drug avoids liver's first pass metabolism.

MATERIALS

Nimesulide, polaxamer 407, polaxamer 188, HPMC and carbopol were purchased from Yarrow chem products, Mumbai. Benzalkonium chloride was purchased from Loba chemie Pvt. Ltd., Mumbai.

METHOD OF PREPARATION

Liquid suppositories were prepared by cold method.[9] Total sixteen formulations (F1-F16) were prepared by using different concentrations of P407 and P188 to study gelation temperature (Table 1). One formulation i.e F14 was selected on the basis of optimum gelationproperty at body temperature (30 ºC-37 ºC). In the optimized formulation, the drug was dispersed with continuous stirring on a magnetic stirrer at room temperature. The dispersion was then cooled to 4 ºC and kept overnight in refrigerator. Mucoadhesive polymers HPMC and carbopol 934P in different concentrations 0.05, 0.075 and 0.1% w/v was then added. Poloxamer 407 and poloxamer 188 are considered in formulation due to its thermosensitive gelation property and maintain the gelation at body temperature.

Table 1: Gelation temperature of combination of P-407 & P-188 studied.

Formulation	Concentration (%w/v)		Gelation Temperature
	P407	P188	
F1	1.0	-	>50ºC
F2	1.5	-	>50ºC
F3	2.0	-	41.9ºC
F4	2.5	-	28.2ºC
F5	-	1.0	>50ºC
F6	-	1.5	>50ºC
F7	-	2.0	>50ºC
F8	-	2.5	>50ºC
F9	2.5	1.0	>50ºC
F10	2.5	1.5	>50ºC
F11	2.5	2.0	>50ºC
F12	2.5	2.5	>50ºC
F13	2.5	0.1	31.6 ºC
F14	2.5	0.3	36.9 ºC
F15	2.5	0.5	43.4 ºC
F16	2.5	0.7	48.7ºC

Table 2: Composition of Nimesulide Liquid suppository from Formulation F1-F7.

Ingredients(%w/v)	F1	F2	F3	F4	F5	F6	F7
Nimesulide	0.1	0.1	0.1	0.1	0.1	0.1	0.1
P-407	2.5	2.5	2.5	2.5	2.5	2.5	2.5
P-188	0.3	0.3	0.3	0.3	0.3	0.3	0.3
HPMC	-	0.05	0.075	0.1	-	-	-
Carbopol934P	-	-	-	-	0.05	0.075	0.1
Benzalkoniumchloride	0.01ml	0.01ml	0.01ml	0.01ml	0.01ml	0.01ml	0.01ml
Distilledwater	Up to10ml	Up to10ml	Up to10ml	Up to10ml	Up to10ml	Up to10ml	Up to10ml

Evaluation of Liquid SuppositorypH

The two areas of critical importance are, effect of pH on solubility and stability. The pH of formulation should be such that the formulation will be stable at that pH and at the same time there would be no irritation to the patient upon administration of the formulation. Rectal liquid suppository formulation should have pH range in between 6.8 to 7.4. The developed formulations were evaluated for pH using control dynamics digital pH meter.[10]

Drug Content

One ml of the solution was pipetted out and dissolved in about 70 ml of phosphate buffer (pH 7.4) in a 100 ml volumetric flask. The flask was shaken for 10 min and volume was made up to the 100 ml mark. Then the flask was kept for 3-4 hr. From the above solution, 1 ml was transferred to a 25 ml volumetric flask and diluted up to the mark with phosphate buffer.[11]

The absorbance of this solution was recorded at 289.5 nm against blank reagent using UV/Vis spectrophotometer.

Gelation temperature

In the measurement of gelation trmperature, 10 ml volume of the liquid suppository was transferred to a 20 ml transparent vial containing a magnetic stirring bar. The vial was heated at an increasing rate of 1°C/min with constant stirring rate at 50 rpm. The temperature at which the rotation of the bar stopped was taken as the gelation temperature.[12]

Measurement of gel strength

Put the liquid suppository in a 50 ml graduated cylinder and gel in a thermostat at 37°C. Place the apparatus for measuring the gel strength (weight 70g) into the liquid suppository. Determine gel strength by the time in seconds that apparatus take to penetrate down through the gel at the bottom of cylinder.[13]

Determination of the mucoadhesive force

The mucoadhesive force, the detachment stress of the liquid suppositories is determined using a modification of the mucoadhesive force-measuring device. Cut a section from the fundus of rabbit rectum and secure instantly with the mucosal side out into each glass vial. Store the vials at 36.5°C for 10 min. Connect one vial to the balance and fix other with the poloxamer gel added and adjust the height so that the gel is placed between the mucosal sides of both vials. The weights were increased in the other side of device until the two vials were detached. Determine mucoadhesive force, the detachment stress (dyne/cm²), from the minimal weights that detach 2 vials.[13]

***In-Vitro* Study**

In-vitro studies were carried out using Keshary-Chein diffusion cell. 1 ml of the liquid suppository was spread uniformly on the cellophane membrane (0.45 µm, Millipore) and then the membrane was affixed in the diffusion cell. Phosphate buffer 7.4 was used as receptor compartment. The donor compartment was kept in contact with the receptor compartment and the temperature was maintained at 37±0.5°C. The solution on the receptor side was stirred by externally driven teflon coated magnetic stirrer using a small bead. With the interval of 0.5 hr, 1 ml of the sample was withdrawn from the diffusion cell and the cells were again replenished with fresh phosphate buffer (pH 7.4) 1 ml. The sample withdrawn was diluted and was analyzed on UV spectrophotometer at 298.5 nm.[14]

RESULTS AND DISCUSSION

pH

pH is the important parameter for mucoadhesive liquid suppositories. The pH of all the formulations was found to be satisfactory and was in the range of 6.6 - 7.2.

% Drug Content

Table 3. below shows the percent drug for formulations F1, F2, F3, F4, F5, F6, F7. The drug content was found to be in acceptable range for all the formulations.

Table 3: % Drug Content.

Formulation	% Drug content
F1	96.14%
F2	95.21%
F3	97.08%
F4	93.98%
F5	95.95%
F6	92.76%
F7	90.30%

Gelation Temperature

Gelation temperature is the temperature at which the liquid phase makes a transition to gel. A gelation temperature range suitable for liquid suppository would be 30–36°C. If the gelation temperature of liquid suppository is lower than 30°C, gelation occurs at room temperature leading to difficulty in manufacturing, handling and administering. If the gelation temperature is higher than 36°, the suppository still stays as a liquid at body temperature, resulting in leakage from the anus. Therefore, liquid suppository must have the suitable gelation temperature between 30–36°, to be in a liquid form at room temperature and to form a gel in the rectum. During preliminary work different concentration of poloxamer 407 and poloxamer 188 was studied to optimum gelation temperature range. When the concentration of mucoadhesive polymers HPMC and carbopol 934P were increase in the formulations, the gelation temperature was decreased. The gelation temperature of all the formulations isshown in table 4,

Table 4: Gelation temperature of formulation (F1-F7).

Sr. No.	Formulation	Gelation Temperature(ºC)
1	F1	36.9
2	F2	34.4
3	F3	34.0
4	F4	33.2
5	F5	34.9
6	F6	31.8
7	F7	29.1

Measurement of gel strength

The gel strength is important in finding the condition which allows the easy insertion of the suppositories and no leakage from the anus. If the gel strength the suppository is low, it would leak from the anus. The

suitable gel strength for the mucoadhesive liquid suppositorieswould be in the range of 10 to 50 seconds.

Addition of mucoadhesive polymers there was increase in the gel strength of the liquid suppositories. With increase in the concentration of the mucoadehesive polymers the gel strength of the liquid suppositories was also increase. Formulations F4, F6 and F7 which containing higher concentration of mucoadesive polymers HPMC and corbopol 934P shown higher gel strength. The results for gel strength of formulations are shown in table 5.

Table 5: Gel Strength of various Formulations.

Sr. No.	Formulation	Gel Strength (sec)
1	F1	16
2	F2	24
3	F3	33
4	F4	47
5	F5	42
6	F6	49
7	F7	58

Mucoadhesive Force

The Mucoadhesive force is an important parameter for in situ gelling rectal suppositories since it prevents the gelled solutions from reaching the end of the colon, the pathway for the first-pass effect. If the mucoadhesive force is too excessive, the gel can damage the rectal mucous membrane. Therefore, liquid suppository must have the suitable mucoadhesive force.The addition of the mucoadhesive polymer reinforced the mucoadhesive force of rectal suppositories which has increased significantly as the concentration of mucoadhesive polymer increased. Formulation F1 show less mucoadhesive force then others formulations because no addition of the mucoadhesive polymer. Increase in the concentration of mucoadhesive polymers in formulations F5, F6 and F7, the mucoadhesive force also increases. The results of mucoadhesive force for formulations are shown in table 6.

Table 6: Mucoadhesive Strength of Prepared Formulations.

Sr. No.	Formulation	Mucoadhesive strength (dyne/cm^2×10^2)
1	F1	21.3
2	F2	52.7
3	F3	93.4
4	F4	109.3
5	F5	88.7
6	F6	114.1
7	F7	138.9

In vitro Study

Seven formulations were evaluated for in *vitro* studies as shown in table 7. All the formulations were studied using the Keshary-Chein diffusion cell. Formulation F1, F2 and F5shows satisfactory % drug release. Increase in the concentration of mucoadhesive polymers results in decrease in release rate.

Table 7: % cumulative drug release of Nimesulide liquid suppositories.

Time(hrs)	Cumulative % drug release						
	F1	F2	F3	F4	F5	F6	F7
0	0	0	0	0	0	0	0
0.5	8.04	9.83	7.24	5.73	6.59	4.83	3.95
1	14.06	12.94	12.26	11.14	10.63	9.36	8.79
1.5	18.37	17.27	17.33	18.77	15.19	12.64	11.83
2	25.98	21.86	26.14	24.83	19.71	17.62	16.25
2.5	32.71	28.65	29.68	30.61	27.55	22.84	21.64
3	39.67	37.62	35.44	37.59	34.78	29.38	25.93
3.5	48.28	43.51	42.79	43.78	45.86	37.75	33.37
4	62.63	55.61	51.94	52.49	57.07	46.88	40.53
4.5	76.61	64.87	63.69	59.24	63.84	55.24	49.01
5	85.98	74.89	71.83	66.32	74.52	67.42	57.68
5.5	96.65	88.17	80.46	75.97	85.97	76.81	69.44

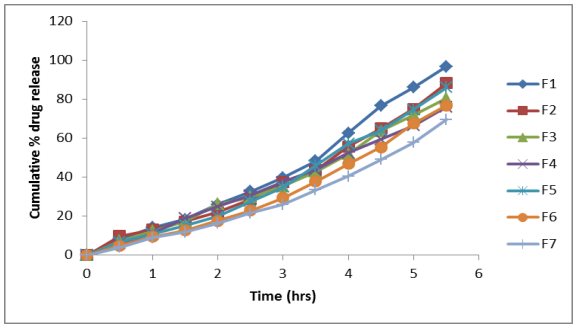

Figure 1: Plot showing *In-vitro* drug release profile of formulations F1-F7.

Table 8: First order drug release kinetic data of formulations F1-F7.

Time(hrs)	Log % drug remaining						
	F1	F2	F3	F4	F5	F6	F7
0	2	2	2	2	2	2	2
0.5	1.963599	1.955062	1.967361	1.974374	1.970393	1.9785	1.982497
1	1.934195	1.939819	1.943198	1.948706	1.951192	1.95732	1.960042
1.5	1.91185	1.917663	1.917348	1.909716	1.928447	1.941313	1.945321
2	1.869349	1.892873	1.868409	1.876045	1.904661	1.915822	1.922985
2.5	1.827951	1.853394	1.847079	1.841297	1.860038	1.887392	1.894094
3	1.780533	1.795045	1.809964	1.795254	1.814381	1.848928	1.869642
3.5	1.713659	1.751972	1.757472	1.749891	1.733518	1.794139	1.82367
4	1.572523	1.647285	1.681784	1.676785	1.632761	1.725258	1.774298
4.5	1.36903	1.545678	1.560026	1.610234	1.558228	1.65089	1.707485
5	1.146748	1.399847	1.449787	1.527372	1.406199	1.512951	1.626546
5.5	0.525045	1.072985	1.290925	1.380754	1.147058	1.365301	1.485153

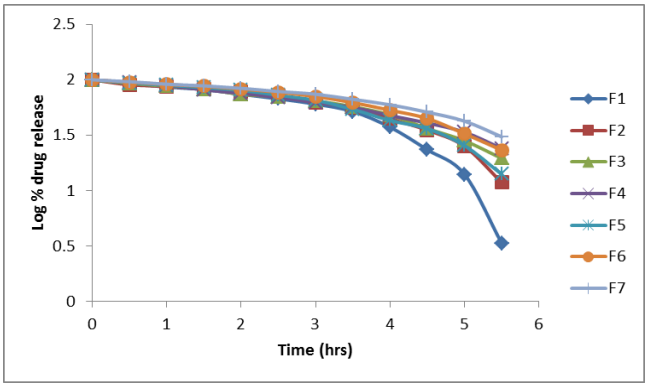

Figure 2: Plot showing first order drug release kinetic data of formulations F1-F7.

Table 9: Higuchi model data of formulations F1-F7.

Timesqrt (hrs)	Cumulative % drug release						
	F1	F2	F3	F4	F5	F6	F7
0	0	0	0	0	0	0	0
0.707107	8.04	9.83	7.24	5.73	6.59	4.83	3.95
1	14.06	12.94	12.26	11.14	10.63	9.36	8.79
1.224745	18.37	17.27	17.33	18.77	15.19	12.64	11.83
1.414214	25.98	21.86	26.14	24.83	19.71	17.62	16.25
1.581139	32.71	28.65	29.68	30.61	27.55	22.84	21.64
1.732051	39.67	37.62	35.44	37.59	34.78	29.38	25.93
1.870829	48.28	43.51	42.79	43.78	45.86	37.75	33.37
2	62.63	55.61	51.94	52.49	57.07	46.88	40.53
2.12132	76.61	64.87	63.69	59.24	63.84	55.24	49.01
2.236068	85.98	74.89	71.83	66.32	74.52	67.42	57.68
2.345208	96.65	88.17	80.46	75.97	85.97	76.81	69.44

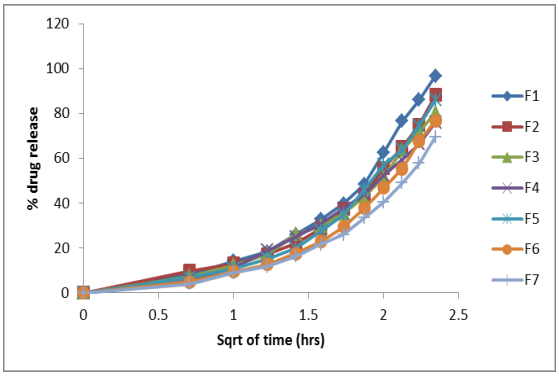

Figure 3: Higuchi release (Cumulative % drug release vs square root of time) offormulations F1-F7.

Analysis of drug release data

To analyse the in vitro release data various kinetic models were used to describe the release kinetics. The zero order rate Eq. (1) describes the systems where the drug release rate is independent of its concentration. The first order Eq. (2) describes the release from system where release rate is concentration dependent. Higuchi (1963) described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion Eq. (3).

$$C = k0t \quad (1)$$

Where, K0 is zero-order rate constant expressed in units of concentration/time and t is the time.

$$LogC = LogC0 - kt / 2.303 \quad (2)$$

Where, C0 is the initial concentration of drug and K is first order constant.

$$Q = Kt1/ 2 \quad (3)$$

Where, K is the constant reflecting the design variables of the system.

Regression Co-efficient (r^2) values obtained from various plots were studied to find the plot showing best linearity of data.

Table 10: Regression Co-efficient (r^2) values of formulations F1- F7.

Kinetics Models	Regression Coefficient (r^2)						
	F1	F2	F3	F4	F5	F6	F7
Zero order	0.9749	0.972	0.985	0.9967	0.9759	0.9663	0.9667
First order	0.7565	0.8239	0.8965	0.938	0.8575	0.8719	0.8868
Higuchi	0.8399	0.8382	0.8668	0.895	0.8352	0.8169	0.8211

Table 10. Illustrates the analysis of release data of nimesulide from different formulations using zero order, first order and higuchi model. In vitro release profiles of the drug from formulations F1-F7 Could be best expressed by Zero order equation, as the plot showed high linearity r^2.

CONCLUSION

In this study, an in situ gelling thermoreversible liquid suppository of nimesulide was developed using poloxamer P407, poloxamer P188 and mucoadhesive polymer (Hydroxy Propyl Methyl Cellulose) and carbopol 934P. The results showed that, gelation temperature decreased upon incorporation of the mucoadhesive polymer in the poloxamer solution. Also polymer addition increases the gel strength and the mucoadhesive force of the prepared solutions. In the in-vitro release study, increase in the concentration of the mucoadhesive polymer leads to decrease in release rate of the drug. Formulations F2 and F5 showed the most promising results for evaluation parameters such as gelation temperature, gel strength, mucoadhesive force and in-vitro release.

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