Original Article

Formulation, Development and Evaluation of Nifedipine Emulgel for Treatment of Anal Fissures using Polymeric Emulsifiers

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ABSTRACT

Aim/Background: Nifedipine (NIF) is act as Calcium channel blocker which belongs to chemical class dihydropyridine and used in the treatment of hypertension. An anal fissure (AF) is the most common anorectal conditions encountered in clinical practice. Patient anal fissures experience anal pain with defecation and minor bleeding. Emulgel formulations are considered a combination of emulsion and gels and emulgel has advantages of both. Emulgels have better penetration of actives than conventional topical formulations. **Materials and Methods:** Emulgel formulations are prepared with the lowest concentration of emulsifiers 1.5-4.0%. Carbomer homopolymer type C used as a polymeric emulsifier while formulating the formulation. The concentrations of Polymeric emulsifiers, high HLB surfactant and low HLB surfactants are varied to two level concentrations two optimize the formulations. Sorbitan monooleate and Polysorbate 20 used as surfactants. **Results:** Emulgel formulations are evaluated for homogeneity, consistency, grittiness, compatibility, pH, Viscosity, drug content, spreadability, extrudability and *in-vitro* drug release from the formulations. The optimized formulation has been charged for stability study at room temperature and accelerated storage condition. Stability results are similar to the initial results. *In-vitro* drug release profile of the initial time point versus 3M stability time point at accelerated and room temperature storage condition is similar. **Conclusion:** Carbomer homopolymer type C can be employeed as polymeric emulsifiers to stabilize unstable to stable emulsion.

Key words: Nifedipine, Polymeric emulsifiers (PE), Anal fissures, Emulgel, Evaluation of emulgel formulation.

INTRODUCTION

Nifedipine belongs to Chemical class dihydropyridine and act as Calcium channel blocker. Nifedipine is widely used in treatment of Ischaemic heart disease, hypertension and related cardiovascular disorders.[1-4] Nifedipine has a modulating effect on the microcirculation. Nifedipine can be used topically in treatment of anal fissures. Nifedipine relaxes and dilates the vascular smooth muscles by inhibiting the calcium ion entry through voltage sensitive area. Nifedipine modulates microcirculation in vascular smooth muscles which helps healing of anal fissures.[5-6]

Anal fissure is a linear tear in the mucosa of the anal canal normally extending distally from the dentate line to the anal verge. An acute tear in the mucosa is analogous to a 'split lip' of the anus; if this fails to heal it progresses to a chronic anal fissure. Patient with anal fissures suffers from significant pain during defecation and minor fresh red bleeding. Anal fissures are commonly seen on the posterior midline but some time can be seen on anterior lines. Major reason for anal fissures is loss of tonicity of the anal sphincter and improper anal blood flow. Current treatment for anal fissures is dietary

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management, oral, injectable, topical medicines, dilation therapy and surgery.[7-9]

Emulgel are emulsions, either oil-in-water or water-in-oil, which are gelled by mixing with a gelling agent. Emulgel is a most promising vehicle for the delivery of hydrophobic drugs. The Emulgel in other words is a combination of Emulsion and Gel.[10-14]

MATERIALS AND METHODS

Material

Nifedipine (Sharon Lab.), Transcutol P(Gattefosse), Butylatedhydroxytoluene (Merck, India), Isoporpyl myristate (Croda, India), Benzyl alcohol (J. T. Baker Ltd), Medium Chain Tri-glycerides (BASF, India), Mineral Oil (BASF, India), Sorbitan oleate (Seppic, France), Polysorbate 20(Seppic, France), Carbomer homopolymer type C (Lubrizol) and Sodium hydroxide (Merck, India).

Method

Preparation of Emulgel

Compositions of all the formulation are tabulated in Table 1.

Aqueous Phase: Carbomer homopolymer type C is dispersed in mixture of polysorbate 20 and purified water under slow stirring. **Drug Phase:** Nifedipine dissolved in mixture of Benzoyl alcohol and Transcutol P under slow stirring. **Oil Phase:** Butylatedhydroxytoluene dissolved in mixture of Isopropyl myristate, mineral oil, sorbitan oleate and Medium chain triglycerides under slow stirring. Drug phase added to oil phase under stirring and mixed the phases properly. Add aqueous phase to this phase and bulk homogenized for 20 min. Add sodium hydroxide solution and homogenize the bulk for 20 min. Mix the bulk under slow stirring for 30 min.

Characterization of Emulgel

Description

The formulated formulations were evaluated for color, homogeneity, consistency, grittiness and phase separation.[15-16]

FTIR Spectra

The IR absorption spectrum of the pure drug was taken in the range of 4000-400 cm^{-1} using KBr pellet method. The major peaks were reported for evaluation of purity. Observed peaks are similar to reported peaks of Nifedipine.[17]

Compatibility Study by FTIR

The IR spectrum of pure drug was taken in range 4000-400 cm^{-1} by KBr pellet method. The observed peaks were evaluated for purity of drug.[17-18]

pH

The pH of the formulation was determined by using digital pH of meter. 1g of each formulation dispersed in 10g of Purified water separately. All the dispersions were shaken properly and determined the pH using digital pH meter.[19-20]

Viscosity

Viscosities of the formulated formulations were determined by BROOKFIELD CAP 2000 plus viscometer.

Table 1: Formulation composition.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Nifedipine	0.30	0.30	0.30	0.30	0.30	0.30	0.30	0.30
Transcutol P	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00
Butylatedhydroxytoluene	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10
Isopropyl Myristate	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00
Benzyl alcohol	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00
Medium Chain Tri-glycerides	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00
Mineral Oil	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00
Sorbitan Oleate	0.50	0.50	0.50	0.50	1.00	1.00	1.00	1.00
Polysorbate 20	3.00	1.50	3.00	1.50	3.00	1.50	3.00	1.50
Carbomer homopolymer type C	1.00	1.00	0.50	0.50	1.00	1.00	0.50	0.50
Sodium hydroxide	QS	QS	QS	QS	QS	QS	QS	QS
Purified water	QS to 100	QS to 100	QS to 100	QS to 100	QS to 100	QS to 100	QS to 100	QS to 100

The method used for determination of viscosities is 100RPM for 1 min Cone spindle 04.[21-23]

Drug Content (Assay)

0.25 gram of formulation was transferred to volumetric flask of capacity of 50ml and diluted to mark with 100% methanol. Further 1ml of solution diluted to 100ml with 100% methanol in volumetric flask. The drug content was determined at 341.2 nm using UV–Vis spectrophotometer.[24-27]

Spread ability by Texture Analyzer

The spread ability of the formulated formulations was determined by texture analyzer. Spread ability is measured in terms of firmness and peak negative force in instruments texture analyzer.[28]

Extrudability

The amount of formulation extruded from Laminated Tube on application of weight (in gm) required to extrude at least 0.5cm ribbon of formulation in 10s was determined.[29-31]

$$\text{Extrudability} = \frac{\text{Applied weight to extrude formulation from tube}}{\text{Area } (\text{cm}^2)}$$

In-vitro drug release study

The *in-vitro* drug release study was carried out using dialysis membrane. Dialysis membrane was cut to suitable size to fix on Franz diffusion cell. First dialysis membrane was boiled in distilled water for 1 hr and in absolute alcohol for next 1 h. Dialysis membrane was soaked in pH 7.4 phosphate buffer saline for 24 h. *In vitro* drug release studies were carried out by taking 500mg of emulgel formulation on the dialysis membrane. Dialysis membrane along with formulation was mounted on the Franz diffusion cell. The receptor medium with pH 7.4 phosphate buffer saline was maintained at constant temperature of 35°C by circulating water bath.[32-38]

Ex-vivo Studies

Ex- vivo skin permeation was performed by Franz Diffusion cell with effective skin diffusion area of 3.56 cm^2. The rat skin of suitable size was mounted between donor and acceptor compartment with the help of clamp. The skin (Dorsal side) should be mounted such that the stratum corneum facing the donor compartment. Than fixed quantity of emulgel containing 1.0% Luliconazole was applied on donor compartment. The receptor compartment was filled with phosphate buffer pH 7.4 was maintained at temperature 35°C with stirring at 100rpm. At predetermined intervals 1hr, 1ml was withdrawn and the same volume of the same medium was added immediately into receptor compartment. The procedure was repeated up to 6hrs. The samples were analyzed by UV spectrophotometer at 296 nm using blank as phosphate buffer pH 7.4.[39-43]

Stability studies of the optimized formulation

The Optimized formulation was packed in High barrier laminated collapsible tubes. Stability study was carried out for 3Months by keeping at 25°C±2°C and 60%±5% RH and 40^0 C±2^0C and 75%±5% RH. Samples were withdrawn at time point 1M, 2M and 3M. Withdrawn stability samples were evaluated for physical appearance, viscosity, drug content, pH and *in vitro* studies through dialysis membrane.[43-46]

RESULTS AND DISCUSSION

Description

All the formulations were yellowish white cream with uniform homogenous mixture with glossy texture. Results are discussed in Table 2.

Table 2: Physical properties of formulations.

Sr. No.	Color	Phase Separation	Grittiness	Homogeneity	Consistency
F1	Yellowish white cream	Yes	-	Poor	Satisfactory
F2	Yellowish white cream	None	-	Fair	Satisfactory
F3	Yellowish white cream	Yes	-	Poor	Satisfactory
F4	Yellowish white cream	None	-	Excellent	Excellent
F5	Yellowish white cream	None	-	Good	Good
F6	Yellowish white cream	None	-	Good	Good
F7	Yellowish white cream	None	-	Good	Good
F8	Yellowish white cream	None	-	Good	Good

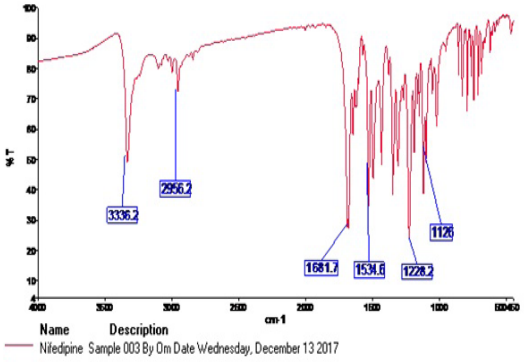

Figure 1: IR Spectra for Nifedipine.

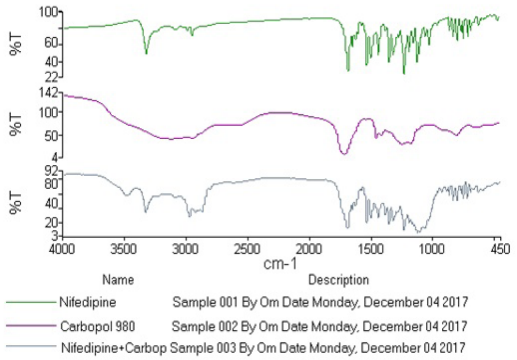

Figure 2: IR Spectra for Nifedipine, Carbopol 980 and combination both.

Table 3: Infra-red Bands for Nifedipine.

IR Bands(cm^{-1})	Types of Vibrations
3336.2	- ArCH. str.
2956.2	-me-ch. Str
1681.7	-C=O str.
1534.6	-C=C str.
1128.2	-C-O str.
1126.0	-C-N str.

All the formulations has color Yellowish white due to Nifedipine is yellow in color. All the formulations were physically stable except two formulations F1 and F3 has shown phase separation. None of the formulation has shown grittiness at initial time point. All the formulations have acceptable homogeneity and consistency.

FTIR Spectra

The major peaks were reported for evaluation of purity. An IR spectrum for Nifedipine has shown in Figure 1. Observed peaks are similar to reported peaks of Nifedipine and peaks are reported in Table 3. A result obtained with IR spectra has shown similar bands to the standard spectra of the Nifedipine. Hence Nifedipine API is identified.

Compatibility Study by FTIR

An IR spectrum is represented in Figure 2. IR Spectra obtained from combination of Nifedipine and Carbopol 980 was concordant with IR spectra of Nifedipine. All the bands of Nifedipine are in combination with Carbopol 980 and nifedipine. Hence Nifedipine has good compatibility with Carbopol 980 Polymer.

pH

pH of the formulations were found in pH range 6.38 to 6.63. Results are discussed in Table 4. This pH range of the formulation lies in the normal pH of the skin and should not produce skin irritation due to pH.

Table 4: pH, Viscosity, Drug content, spreadability and extrudability results for all formulations.

Sr. No.	pH	Viscosity	Drug Content	Spreadability	Extrudability
F1	6.52	1.23	97.6	10.056	++
F2	6.60	2.45	98.9	14.908	++
F3	6.44	1.41	98.3	12.453	++
F4	6.41	4.48	99.9	16.245	+++
F5	6.63	5.87	100.4	13.754	++
F6	6.56	3.12	101.1	13.169	+++
F7	6.48	5.01	100.9	13.987	+++
F8	6.38	3.89	99.4	15.567	+++

+++ indicates excellent, ++ Indicates good, + Indicates poor

pH of the all formulation has shown slight variation, it may be due to concentration of Carbopol 980 in formulation. Carbopol 980 is acidic in nature. More the concentration of carbopol more will be the pH and vice a versa.

Viscosity

Viscosity of the formulations has shown variations among the different formulations. Viscosity of the formulations is in range of 1.23 to 5.87. Results are discussed in Table 4. Viscosity of the formulation is dependent on the concentration of carbopol 980, physical stability of the formulation and pH of the formulation. Increase in concentration of Carbopol 980, viscosity of the formulation increases. Carbopol 980 is pH dependant polymer. Hence pH of the formulation increases, viscosity will also increase. If physical stability of the formulation increases then viscosity of the

formulation will also increases. More the stable formulation more will be the viscosity. F4 formulation has optimum viscosity with good spread ability.

Drug Content (Assay)

Drug Content (Assay) of the formulation is ranges from 97.6 to 101.1. Results are discussed in Table 4. Drug content is dependent upon the drug addition and uniform mixing of drug in formulation. All the assay of the formulations lies in the acceptable range, to have better efficacy of the formulation.

Spread ability by Texture Analyzer

Spread ability of the formulation is found in range 10.056 to 16.245. Results are discussed in Table 4. Formulation F4 has better spred ability than rest of the formulation. Formulation F1 has less spread ability than rest of the formulations.

Extrudability

Formulations F4, F6, F7 and F8 have excellent Extrud ability and formulation F1 and F2 has good extrudability. Results are tabulated in Table 4. All the formulations are easily removable from Laminated tube.

In-vitro drug release study

Release profiles of all the formulations were tabulated in Table 5 and graphically represented in Figure 3. Formulation F1, F2 and F6 has shown less drug release from the formulation. Formulation F3 and F4 has shown initially rapid release of drug from formulation and after 2 hrs very low drug release from formulation. Formulation F 5 has initial constant release till 4hr, burst release at 6 hrs and then again constant drug release after 6hr. Formulation F4 and F5 has constant drug release profile till 12hr. Formulation F4 has better drug release profile than F7.

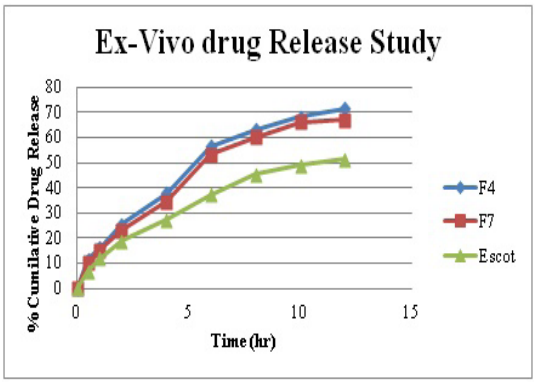

Figure 3: Comparative *in-vitro* drug release profile from all formulations.

Ex-vivo Drug Release study

Two formulations F4 and F7 were selected along with marketed formulation Escot Cream for the *ex-vivo* study among all the formulation. Results are discussed in Table 6 and graphically represented in Figure 4. Formulations F 4 and F7 found good *in-vitro* drug release profile because of this; these two formulations were employed in *ex-vivo* studies. An *ex-vivo* study has shown formulation F4 has better drug release profile than the formulation F7 and Escot cream. But formulation F7 has better permeation than the marketed formulation Escot Cream. Similar results were obtained in *in-vitro* drug release study.

Stability studies of the optimized formulation

Stability results of the all the formulations are tabulated in Table 7. Formulation is stable for 3months at storage condition 40^0C/75%RH and 25^0C/60%RH. All the physical parameters shows similar results at stability time point when compared with initial results. Viscosity and pH of the optimized formulation is stable for 3 months. Drug content in formulation throughout the

Table 5: *In-vitro* drug release study for all the formulations.

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
0.5	10.12	12.63	9.19	14.68	11.76	9.26	13.67	25.15
1	15.56	17.87	31.56	19.19	17.67	12.45	21.23	56.76
2	21.45	22.32	35.16	27.39	25.98	18.28	28.19	58.19
4	28.98	30.12	37.46	42.27	36.72	27.14	40.12	59.87
6	37.51	38.97	40.82	56.64	44.18	34.38	54.32	60.12
8	45.17	46.18	41.29	62.02	56.64	42.36	59.98	61.45
10	51.87	59.87	42.34	68.18	63.34	48.94	65.66	62.23
12	58.19	67.23	45.57	74.47	70.45	54.73	71.54	63.29

Table 6: *Ex-vivo* drug release study for the formulations F4 and F7.

Time (hr)	F4	F7	Escot Cream
0	0	0	0
0.5	11.71	10.23	6.78
1	16.13	15.17	12.05
2	25.32	23.01	18.98
4	37.87	34.38	27.23
6	56.49	53.12	37.33
8	63.27	59.98	45.46
10	68.34	66.09	48.93
12	71.67	67.12	51.35

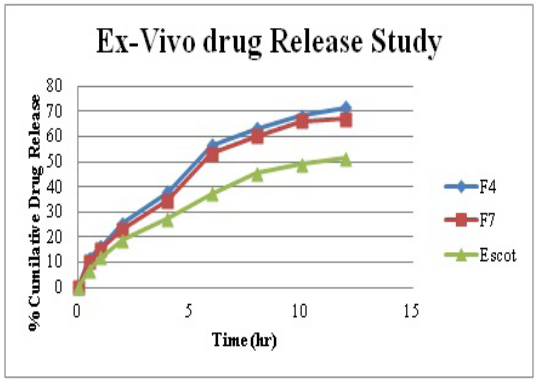

Figure 4: Comparative *in-vitro* drug release profile from all formulations.

Table 7: Stability results for optimized formulation F4.

Batch No.	Initial	40◦C/75%RH			25◦C/60%RH		
		1M	2M	3M	1M	2M	3M
Description	Yellowish white cream	Yellowish white cream	Yellowish white cream	Yellowish white cream	Yellowish white cream	Yellowish white cream	Yellowish white cream
Viscosity	5.87	5.52	5.35	5.24	5.67	5.71	5.51
pH	4.63	4.51	4.48	4.41	4.61	4.58	4.69
Drug Content	100.4	99.4	99.1	98.9	100.1	99.8	99.3
Spread ability	13.754	12.890	12.298	12.183	13.482	13.621	12.769
Extrudability	Excellent	Excellent	Excellent	Excellent	Excellent	Excellent	Excellent

Table 8: *In-vitro* drug release study for Stability samples of optimized formulations.

Time (hr)	F4 Initial	F5 40◦C/75%RH	F6 25◦C/60%RH
0	0	0	0
0.5	14.68	15.12	13.89
1	19.19	22.18	20.62
2	27.39	26.89	26.59
4	42.27	40.73	41.86
6	56.64	58.34	59.22
8	62.02	64.23	65.74
10	68.18	70.23	69.89
12	74.47	76.41	75.13

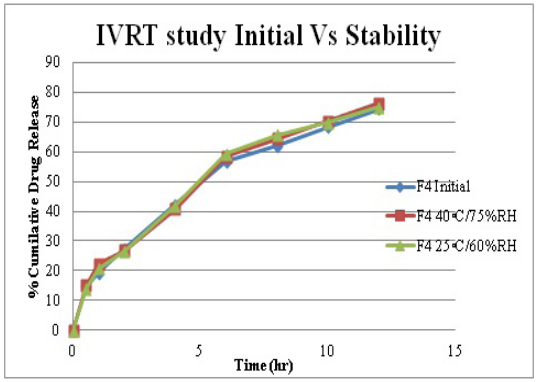

Figure 5: Comparative *in-vitro* drug release profile for Initial vs stability samples.

stability is constant and it does not show significant change. Spread ability and extrudability of the formulation is stable for 3 months at room temperature and accelerated storage condition.

Results for *in-vitro* drug release study for stability samples of optimized formulations are tabulated in Table 8 and presented in Figure 5. 3M stability samples at storage condition 40°C/75%RH and 25°C/60%RH has similar drug release profile to the Initial time point drug release profile. Drug release profiles of initial samples verses stability time point is represented in Figure 5.

CONCLUSION

Polymers act as polymeric emulsifiers. The stable formulation can be formulated with transcutol P, Butylated hydroxytoluene, Isopropyl Myristate, Benzyl alcohol, Medium Chain Triglycerides Mineral Oil, Sorbitan Oleate, Polysorbate 20, Carbomer homopolymer type C, Sodium hydroxide and Purified water. Nifedipine has good compatibility with carbomer homopolymer type C. Pure Nifedipine spectra and sample nifedipine spectra show the similar bands, hence nifedipine is identified in the sample. All the formulations were having acceptable

homogeneity and consistency. pH of the formulation ranges from 6.38 to 6.63. Viscosity, extrudability and spreadability of the formulation were found satisfactory. Formulation F4 and F7 have higher drug release among all the formulation but F4 has slightly more drug release than F7. In the *ex-vivo* study, the formulation F4 has better drug release than formulation F7. Formulation F 4 and F7 have better drug release than currently marketed formulation Escot Cream. Formulation of Nifedipine in emulgel formulation can have better penetration and efficacy. Formulation is stable for 3M at room temperature and accelerated storage condition.

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CONFLICT OF INTEREST

The authors indicate that there is no conflict of interests.

ABBREVIATIONS

NIF: Nifedipine; **AF:** Anal Fissures; **PE:** Polymeric emulsifiers; **HLB:** Hydrophilic-lipophilic Balance; **BHT:** Butylatedhydroxytoulene; **IPM:** Isopropyl myristate; **MCT:** Medium chain triglycerides; **Span 80:** Sorbitan Mono-oleatee; **KBr:** Potassium Bromide; **cm:** Centimeter; **RPM:** Revolutions per minutes; **min:** Minutes, **ml:** Milliliters, **nm:** Nanometer; **UV:** Ultra-voilet; **gm:** Gram; **hr:** hour; **M:** Month; **IR:** Infra-red; **FTIR:** Fourier transform Infra-red; **Carbopol 980:** Carbomer homopolymer type C; **Escot:** Marketed formulation; **RH:** Relative humidity.

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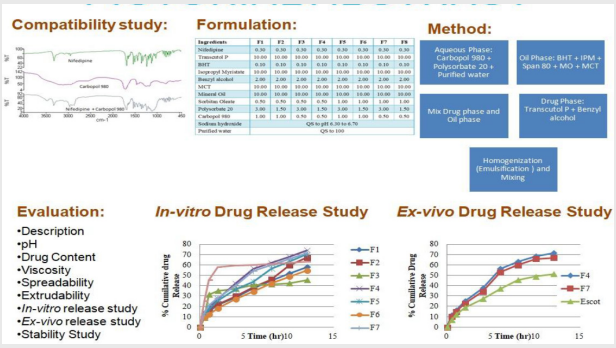
PICTORIAL ABSTRACT



SUMMARY

- Attempt made to formulate the emulgel formulation with lower concentration of emulsifiers. The concept of Polymeric emulsifier is used to stabilise the unstable emulsion to stable emulsion using polymeric emulsifiers. The formulation is prepared using oils, emulsifiers (Polysorbate 20 and Span 80) and Carbomer homopolymer type C as polymeric emulsifiers.
- The formulations were evaluated for physical, chemical properties and drug release properties.
- The emulgel formulation has shown good stability, *in-vivo* and *ex-vivo* drug release. The *in-vitro* drug release is constant after 3months at room temperature and accelerated storage condition.

ABOUT AUTHORS

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Om Shelke, Ph D scholar with 6 years of reach industrial experience in formulation and development. He have good experience in handling semisolid/ topical/ dermal dosage forms for US market (ANDA/NDA). He have good knowledge in Quality by design concept.

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