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Development and Evaluation of Innovative Two- Phase Systems (Bigels) Containing Propionic Acid Derivative for Topical Drug Delivery

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Abstract

Objectives

In the present dissertation work, an attempt was made to develop and evaluate innovative two- phase systems (bigels) containing propionic acid derivative for topical drug delivery having good consistency, possess the advantages of two gels and mask the demerits of individual gels such as organogel and hydrogel.

Methods

Bigel containing Ketoprofen were prepared by mixing of organogel and hydrogel in appropriate ratio. Organogel and hydrogel was characterized. Formulation OG3 from organogel and HG3 from hydrogel was selected as optimized formulations and was used for the preparation of bigel. The prepared bigel was characterized and evaluated for gel-sol transition temperature, drug content determination, *in vitro* drug release studies, *ex vivo* permeation studies.

Results and Discussion

The results of FTIR analysis showed that there was no chemical interaction between drug and excipients. All formulations of bigel showed extended release out of which formulation BG3 was selected as the optimized formulation on the basis of evaluation parameters. *In vitro* permeation release was found to be 98.83% at the end of 8 hrs. *Ex vivo* drug release was found to be 84.66% at the end of 8hrs. The release kinetics of ketoprofen bigel followed Higuchi model.

Conclusion

The study indicated that Bigel containing Ketoprofen (BG3) having good consistency which provides good visual appearance and also BG3 has got required viscosity, spreadability and extrudability. The pH of the formulation BG3 was found to be neutral which is best suited for topical formulations. Based on the encouraging results bigels containing ketoprofen can be used as extended release system.

Keywords: Ketoprofen; Organogel; Hydrogel; Bigel; Pluronic lecithin; HPMC; Topical drug delivery

INTRODUCTION

Topical drug delivery is the most commonly used drug delivery due to the high patient compliance. When compared to other conventional method due to some reasons such as pain less application, easy to apply, do not required any help for administration, avoid first pass metabolism, it can be applied to all types of patients regardless of age etc. Such merits made this topical route of administration one of the best in medical field [1].

Gels are semisolid formulations which usually have two components, liquid and solid. Where liquid component is called solvent and the solid component is called gelling agent/ gelator. On the basis of polarity of solvent, gels are classified in to 2 types: - hydrogel and organogel. The hydrogels are 3D hydrophilic networks of homopolymeric or heteropolymeric chains and the cross-linked hydrogels have the capability to absorb large amount of water without itself dissolving in it. These formulations have high patient compliance because of its interesting properties such as easy removal after the application of the gel, cooling effect, etc. On the other hand, these systems are not effective in delivering hydrophobic drugs across the stratum corneum of the skin due to their less skin permeation. Organogel is a solid like system in which the organic liquid is entrapped inside a thermoreversible 3D network. Organogels are easy to prepare and its lipophilic nature will enhance the drug penetration through the stratum corneum. Organogel is oily in nature so it is very difficult to remove when it is applied to the skin [44,45,4,40,41].

Bigels are gels formed by the combination of two gels ie; organogel and hydrogel. Hydrogels are polar and organogels are non-polar, so bigel consist of both internal and external immobilized phases. The immobilization of the external phase arrests the motion of the internal phase, and hence the chance of coagulation of the internal phase is totally eliminated. If the external phase of the bigels is externally cross-linked, it results in the formation of a permanent bigel. Hydrogel helps in hydration of stratum corneum and organogel helps in increased penetration. Other benefits of bigels include easy washability, easy spreadability, good contact period, accommodate both lipophilic and hydrophilic drugs, provides controlled drug delivery, good moisturizing effect to the skin and bigels can overcome the demerits of both gels which includes the limited ability to cross the lipophilic barrier and low patient compliance for hydrogels and oily residues and stickness of organogel. The main problem of the bigel is destabilization at high temperature, it means that this bigel system is not thermoreversible [1,3,14,27].

According to the distribution of two phases in bigels, these system are mainly classified in to 3 types:-

1. **Hydrogel in organogel type**- it can be defined as the system in which hydrogel phase is distributed within the continuous phase.
2. **Organogel in hydrogel type**- it can be defined as the system which contains organogel as a dispersed phase and hydrogel as a continuous phase.
3. **Bi- continuous/ matrix in matrix type**- it can be regarded as a system with complex structure in which it is difficult to identify the dispersed and continuous phase[45].

MATERIALS AND METHODS

Materials:

Ketoprofen and HPMCK4M were purchased from Balaji Enterprises, Gujarat, India. Pluronic F127, Soyalecithin, Potassium sorbate, Isopropyl palmitate were purchased from Yarrow Chem Products, Mumbai, India.

Methods:

ANALYTICAL METHODS

Determination of λmax for pure drug Ketoprofen

Preparation of stock solution

Accurately weighed 100 mg of Ketoprofen was dissolved by using phosphate buffer of pH 7.4 and made the volume upto 100 ml using same buffer, to produce the stock solution of concentration 1000 µg/ml. The resulting solution was scanned between 200 to 400 nm. Ketoprofen shows an absorbance peak at 260 nm.

Preparation of standard calibration curve of Ketoprofen in pH 7.4 phosphate buffer

From the above standard stock solution of Ketoprofen in pH 7.4 phosphate buffer, aliquots of 4, 6, 8, 10 and 12 ml were transferred to 100 ml volumetric flask and diluted with pH 7.4 phosphate buffer, so that the solutions having concentrations of 40, 60, 80, 100 and 120µg/ml respectively. The absorbance was measured using UV spectrophotometer at 260 nm against pH 7.4 phosphate buffer as blank.

PREFORMULATION STUDIES

Organoleptic evaluation

The organoleptic characters of drug was evaluated and recorded by using descriptive terminology. Following organoleptic properties were studied: colour, odour, taste.

Determination of melting point

Melting point of Ketoprofen was determined by capillary method. The finely ground powder was filled in to capillary tube which was close at one end. The capillary tube was inserted in to the melting point apparatus. The temperature at which the sample gets melted was noted, which gives the melting point of the sample[75].

Determination of solubility

Solubility test of Ketoprofen was performed by using various solvents as distilled water, ethanol, chloroform and ether[76, 77].

Drug- Excipient Compatibility Studies

FTIR: Integrity of the drug in the formulation was checked by taking an IR spectrum of the selected formulation along with the drug and other excipients. The spectra were taken by using Shimadzu IR prestige- 21 Spectrometer and were compared with standard spectra. In this study, palletisation of potassium bromide (KBr) was employed. Before forming the pellet of potassium bromide, it was completely dried at 1000 C for one hour and after drying it was thoroughly mixed with the sample in the ratio of 1 part of sample and 100 parts of KBr. The mixture was compressed to form a disc using dies. This disc was placed in the sample chamber and a spectrum was obtained through the software program which was obtained through the software program which was further subjected to interpretation.

FORMULATION DEVELOPMENT OF KETOPROFEN BIGEL

COMPOSITION OF KETOPROFEN BIGEL

Table 1: Formulation chart of pluronic lecithin organogel

Components	Contents	OG1	OG2	OG3	OG4	OG5
Oil phase	Soya lecithin (gm)	1.25	1.25	1.25	1.25	1.25
	Potassium sorbate (gm)	0.05	0.05	0.05	0.05	0.05
	Isopropyl palmitate(ml)	12.50	12.50	12.50	12.50	12.50
Aqueous phase	Pluronic F127 (gm)	1.25	2.50	3.75	5.00	6.25
	Potassium sorbate (gm)	0.05	0.05	0.05	0.05	0.05
	Distilled water (ml)	12.50	12.50	12.50	12.50	12.50

Table 2: Formulation chart of hydrogel

Contents	HG1	HG2	HG3	HG4	HG5
HPMC K4M (gm)	1	1.5	2	2.5	3
Distilled water (ml)	25	25	25	25	25

Table 3: Formulation chart of bigel

Contents	BG1	BG2	BG3	BG4	BG5
Drug (gm)	5	5	5	5	5
Hydrogel(gm)	25	35	45	55	65
Organogel(gm)	70	60	50	40	30

METHOD OF PREPARATION OF BIGEL

The preparation of bigel involves three steps as they consist of two individual gels in making, the steps are

- Preparation of organogel
- Preparation of hydrogel
- Mixing of hydrogel and organogel to form bigel

Preparation of pluronic lecithin organogel

The organogel involves two phase, one is the aqueous phase and the other is the oil phase.

Preparation of aqueous phase:

Required amount of pluronic F127 was added to cold water and was allowed to soak for 1 hr under cold temperature. Then the sample was taken and continuously stirred and this mixture was stored in refrigerator for 24 hrs to obtain clear solution. Potassium sorbate in required quantity was added as a preservative[33-37,43-49].

Preparation of oil phase:

Required amount of soya lecithin was weighed and taken in a beaker and dissolved in required quantity of isopropyl palmitate with continuous stirring. Potassium sorbate was added as a preservative and this solution was kept it for 24 hrs at room temperature[50-59].

Preparation of organogel by mixing of oil phase with aqueous phase:

The oil phase was then added in little amount to the aqueous phase with continuous stirring until whole the volume was added[16,23,53,73].

Preparation of hydrogel

HPMC was the polymer used for the preparation of hydrogel. Required quantity of HPMC was added with distilled water and allowed for soaking. After 1 hr the dispersion was mixed continuously in order to obtain a uniform gel[1,4,11,12].

Preparation of ketoprofen bigel

Mixing of organogel and hydrogel to form bigel, it is the most important step in the formation of bigel. The optimised formulation from organogel and hydrogel was taken for the preparation of bigel. Required amount of the optimised hydrogel and organogel were taken and then mixed according to the ratio required. The process was continued until a creamy white colour uniform gel was obtained. Then the required amount of the drug was dissolved in very less amount of ethanol, this mixture was then mixed thoroughly for uniform dispersion[5,17,20,22,60-68].

CHARACTERIZATION OF ORGANOGEL AND HYDROGEL

Physical appearance

Physical appearance of the formulated gels was evaluated by visual inspection. Parameters such as consistency, colour and transparency was analysed.

pH

pH of all the formulations was determined by placing an electrode of the digital pH meter on surface of the prepared gel and then to equilibrate for 1 min and reading was taken.

Viscosity

Viscosity of the formulated gels was determined by using Brookfield viscometer (Brookfield DV-II+ Pro). The samples to be analyzed were taken in a 25 ml beaker. The viscosity of the samples was measured by using spindle number 96. The test was repeated 6 times for each sample and the average value was calculated. The test was conducted at room temperature and angular velocity was kept at 10 rpm.

Spreadability

Spreadability of the formulated gels was measured by using two glass plates and a weight to be kept. A circle of 1 cm was premarked on the glass plate into which 0.5gm of gel was placed. On the top of this glass plate a similar glass plate was placed. The 1000 g weight was kept on the upper glass plate for 5 min. The increased diameter caused by the spreading of the gel is measured [1, 4, 16].

Extrudability test

Extrudability test of all the prepared formulations was done by using monsanto hardness tester. The weighed 15 gm of the gel was inserted in the collapsible aluminum tube and the end of the tube was crimped. Then this aluminum tube was placed in the monasanto tester and plunger of the tester was adjusted to hold the tube properly. 1 kg/cm2 pressure was applied to it for 30 sec. The amount of formulation extruded out was weighed[72,74].

CHARACTERIZATION AND EVALUATION OF KETOPROFEN BIGEL

Physical appearance

Physical appearance of the formulated gels was evaluated by visual inspection. Parameters such as consistency colour and transparency was analyzed.

pH

pH of all the formulations was determined by placing an electrode of the digital pH meter on surface of the prepared gel and then to equilibrate for 1 minute and reading was taken.

Viscosity

Viscosity of the formulated gels was determined by using Brookfield viscometer (Brookfield DV-II+ Pro). The samples to be analyzed were taken in a 25 ml beaker. The viscosity of the samples was measured by using spindle number 96. The test was conducted at room temperature and angular velocity was kept at 10 rpm.

Spreadability

Spread ability of the formulated gels was measured by introduction of 0.5gm formulated gel inside a circle of 1cm diameter premarked on a glass plat. On the top of this glass plate a similar glass plate was placed. The 1000 g weight was kept on the upper glass plate for 5 min. The increased diameter caused by the spreading of the gel was measured.

Extrudability test

Extrudability test of all the prepared formulations was done by using Monsanto hardness tester. The weighed 15 gm of the gel was inserted in the collapsible aluminum tube and the end of the tube was crimped. Then this aluminum tube was placed in the monsanto tester and plunger of the tester was adjusted to hold the tube

properly. 1 kg/cm2 pressure was applied to it for 30 sec. The amount of formulation extruded out was weighed and the procedure was repeated.[1,2,3,4,5].

Gel-sol transition temperature

Gel-sol transition temperature of all gels was determined by incubating the formulated gels in a constant temperature bath ranging from 25 ^{0}C – 60 ^{0}C. Within a 5 min interval the temperature of the water bath was increased with and increment of 5 ^{0}C. The temperature was noted at which the gel started to flow when the beaker was inverted [1].

Drug content determination

Drug content of different formulations was calculated using UV spectrophotometer. Gel (100mg) was dissolved in 100 ml buffer and filtered. After filtration the drug content was found out by taking absorbance at λmax 247nm [8].

***In vitro* drug release**

In vitro drug release studies were conducted in modified in vitro permeation apparatus using a cellophane membrane. Phosphate buffer pH 7.4 is the dissolution medium used in the study. Cellophane membrane obtained for the study was soaked in phosphate buffer pH 7.4 overnight. Bigel was accurately weighed and placed over the center portion of the cellophane membrane and this cellophane membrane was tied to one of the opening end of the specially designed hollow glass cylinder. The glass cylinder was then attached to the metallic shaft and then dipped in a way that the membrane just touches the surface of 50 ml phosphate buffer pH 7.4 kept in the beaker. The dissolution medium was kept at a temperature of 37± 0.5 ºC and stirred throughout the studies using a magnetic stirrer at 50 rpm and this condition was maintained till the end of the experiment. In a specified time interval aliquots of 3 ml sample from the receptor medium was withdrawn and filtered. Each filtered sample was diluted and the absorbance was measured by UV spectrometer at 247 nm [1].

Kinetic study

Release kinetics of drug from the dosage form was determined by various mathematical models such as zero order, first order, Korsmeyer- peppas and higuchi model.

1. Cumulative percent drug released Vs time (zero order plots)
2. Log cumulative percent drug remaining Vs time (first order plots)
3. Cumulative percent drug release Vs square root of time (higuchi plots)
4. Log cumulative percent drug release Vs log time (Korsmeyer- peppas plots)

***Ex-vivo* permeation studies**

Modified *ex-vivo* permeation apparatus was used for the *ex-vivo* drug release study using pig ear skin membrane. The dissolution medium used in this procedure is phosphate buffer. Pig ear skin which was collected from the local slaughter house and was cleaned properly. The collected skin was cut in suitable size was stored at -20 ºC. Before the permeation study was started the pig ear skin which was stored in a freezer was taken out and allowed to come into room temperature. 1 gm of the bigel was weighed accurately and placed over the center portion of the excised pig ear skin and tied to the specially designed hollow glass cylinder. The glass cylinder was then attached to the metallic shaft and then dipped in a way that the membrane just touches the surface of 50 ml phosphate buffer pH 7.4 kept in the beaker. Temperature of dissolution medium was kept at 37± 0.5 ºC throughout the experiment and was stirred at 50 RPM using a magnetic stirrer. In a specified interval 3 ml sample was taken from the receptor medium and filtered. Samples again diluted and analyzed by UV spectrometer at 247 nm [1,26].

RESULTS AND DISCUSSIONS

DEVELOPMENT OF ANALYTICAL METHODS

Determination of λmax for pure drug Ketoprofen

The absorbance maxima of pure drug Ketoprofen was determined and maximum absorbance was shown at 260nm. This wave length is used for the construction of standard curve for estimation of the drug.

Standard calibration curve of Ketoprofen in pH 7.4 phosphate buffer

The standard calibration curve of Ketoprofen was determined the obtained results were used to plot a graph with absorbance V/s concentration. It gave straight line that passes through the origin.

Table 4: Data for standard calibration curve of ketoprofen in pH 7.4 phosphate buffer

Concentration (µg/ml)	Absorbance (at 260nm)
0	0
40	0.223
60	0.350
80	0.463
100	0.605
120	0.732

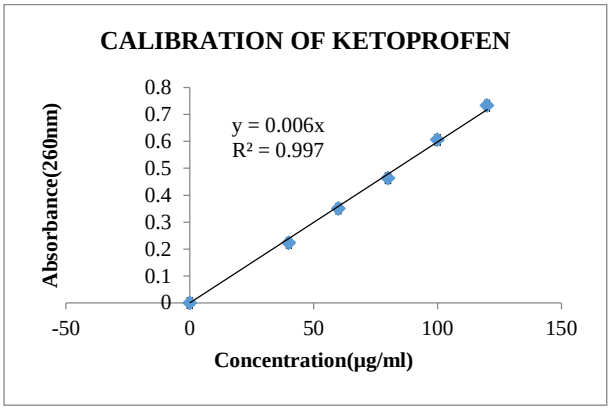

Figure 1: Standard calibration curve of Ketoprofen in pH 7.4 phosphate buffer

PREFORMULATION STUDY

Organoleptic evaluation

Table 5: Organoleptic characters of Ketoprofen

Colour	White powder
Odour	Odourless
Taste	Bitter

Determination of melting point

The melting point of Ketoprofen was obtained at 94 ^{0}C.

Determination of solubility

The ketoprofen was freely soluble in ethanol (95%), chloroform, ether and insoluble in water.

Drug- Excipient Compatibility Studies

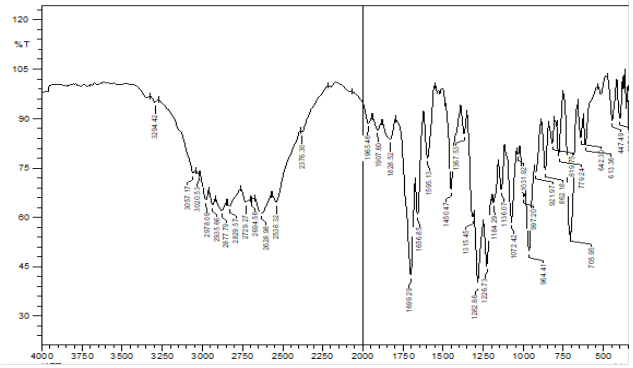

Figure 2: FTIR Spectrum of Ketoprofen

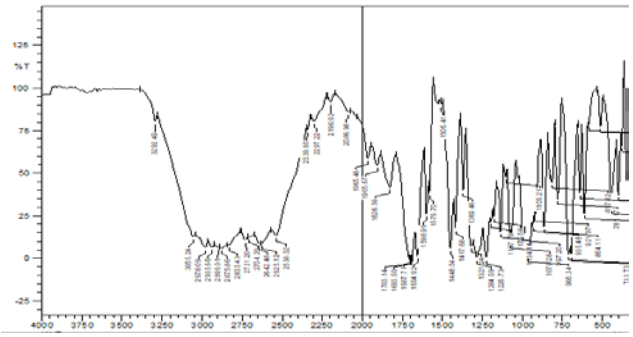

Figure 3: FTIR Spectrum of Ketoprofen + HPMCK4M

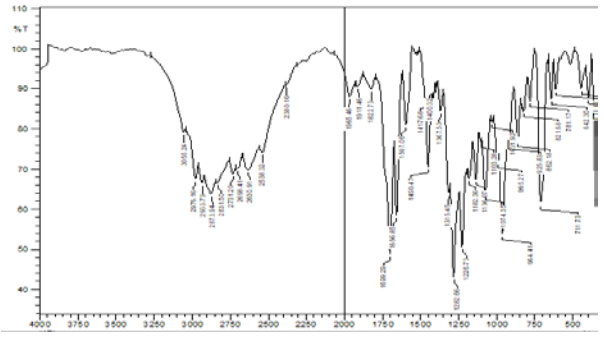

Figure 4: FTIR Spectrum of Ketoprofen + Pluronic F127

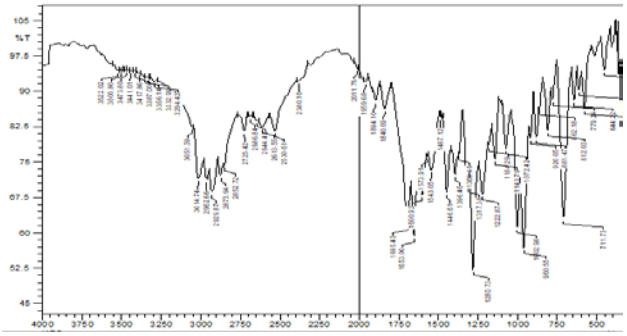

Figure 5: FTIR Spectrum of Ketoprofen + Potassium sorbate

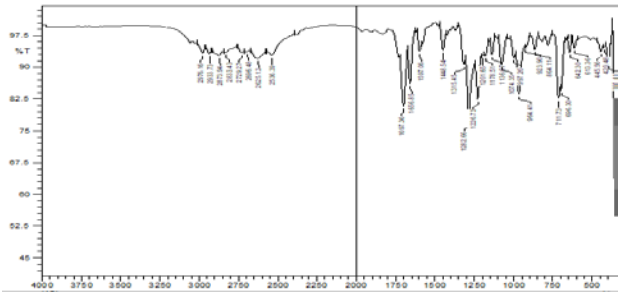

Figure 6: FTIR Spectrum of Ketoprofen + Soya lecithin

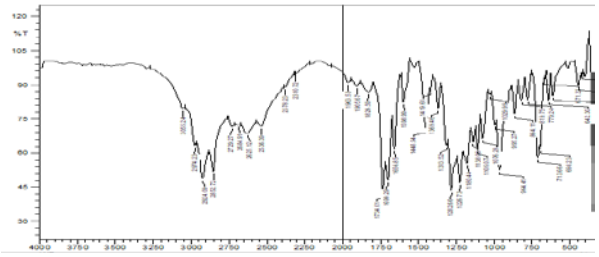

Figure 7: FTIR Spectrum of Ketoprofen + Isopropyl palmitate

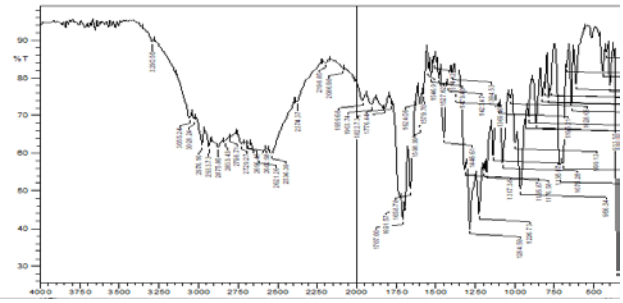

Figure 8: FTIR Spectrum of Ketoprofen + Ethanol

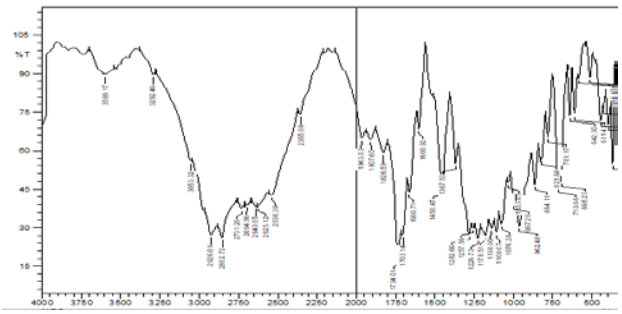

Figure 9: FTIR Spectrum of Ketoprofen + Excipients

The interpretation of FTIR spectrum of Ketoprofen was given in table 6.

Table 6: Spectral analysis of Ketoprofen

Sl. No	Functional group	Characteristic peak range in cm-1	Characteristic peak in cm-1
1	Aromatic C=C	1500- 1600	1595.13
2	Aromatic C–H	3010- 3100	3057.17
3	C=O	1600- 1900	1699.29
4	COOH	1050- 1300	1072.42
5	C–H	2850- 2970	2877.79

The FTIR spectrum of the drug, Ketoprofen shows prominent peaks with respect to functional groups. No peak change was obtained in the physical mixture of drug with excipients. So it was concluded that there is no significant interaction between them.

FORMULATION DEVELOPMENT

Figure 10: Organogel

Figure 11: Hydrogel

Figure 12: Ketoprofen Bigel

CHARACTERIZATION OF ORGANOGEL

Physical appearance

Physical appearance of the formulation is an important parameter for topical delivery as it affects the patient compliance. All formulations were subjected to visual appearance on the basis of transparency, colour and consistency. All formulation was found to be non-transparent, off white in colour and creamy in consistency.

pH

The pH obtained was within topically accepted range so it would not cause any irritation on skin.

Table 7: pH of formulated organogel

Formulation code	pH*
OG1	6.8±0.1
OG2	7.1±0.3
OG3	7.4±0.1
OG4	5.7±0.2
OG5	5.5±0.1

Viscosity

The viscosity of the organogel gradually increased from formulation OG1 to OG5. This gradual increase was based on the concentration of pluronic added to the formulation. Concentration of pluronic in the formulation was directly proportional to the viscosity of the formulation.

Table 8: Viscosity of formulated organogel

Formulation code	Viscosity *(cps)
OG1	4202±0.2
OG2	4332±0.1
OG3	4507±0.1
OG4	4510±0.3
OG5	4764±0.2

Spreadability

The spreadability of the formulated organogel found that the formulation OG1 has the highest spreadability and formulation OG5 has the least spreadability. The amount of the polymer added to the formulation determines the integrity and viscosity of the formulation. The formulation OG5 with highest viscosity showed least spreadability and the formulation OG1 with least viscosity showed high spreadability.

Table 9: Spreadability of formulated organogel

Formulation code	Spreadability*(mm)
OG1	17.24±0.2
OG2	16.23±0.1
OG3	15.20±0.2
OG4	12.98±0.1
OG5	10.46±0.1

Extrudability

The extrudability of the formulated organogels was determined and it was found that OG1 has got the highest extrudability and OG5 has got the least extrudability. The

formulation OG5 with highest viscosity showed least extrudability and the formulation OG1 with least viscosity showed highest extrudability.

Table 10: Extrudability of formulated organogel

Formulation code	Extrudability (gm/sec)
OG1	1.49±0.3
OG2	1.38±0.2
OG3	1.33±0.1
OG4	1.26±0.1
OG5	1.14±0.2

CHARACTERIZATION OF HYDROGEL

Physical appearance

Physical appearance of the formulation is an important parameter for topical delivery as it affects the patient compliance. All formulations were subjected to visual appearance on the basis of transparency, colour and consistency. All formulations were found to be transparent, colourless and smooth in consistency.

pH

The pH obtained was within topically accepted range so it would not cause any irritation to the skin.

Table 11: pH of formulated hydrogel

Formulation code	pH*
HG1	6.9±0.1
HG2	7.2±0.2
HG3	7.4±0.1
HG4	5.7±0.2
HG5	5.5±0.1

Viscosity

The viscosity of the formulated hydrogel was measured using Brooksfield viscometer. The viscosity of hydrogel gradually increased from formulation HG1 to HG5. The formulation HG1 shows showed least viscosity and the formulation HG5 showed the highest viscosity.

Table 12: Viscosity of formulated hydrogel

Formulation code	Viscosity*(cps)
HG1	3148±0.1
HG2	3422±0.2
HG3	3605±0.3
HG4	3770±0.1
HG5	3910±0.1

Spreadability

The spreadability of the formulated hydrogel was measured and it was found that the formulation HG1 has the highest spreadability and formulation HG5 has the least spreadability. The formulation HG5 with highest viscosity showed least spreadability and the formulation HG1 with least viscosity showed higher spreadability.

Table 13: Spreadability of formulated hydrogel

Formulation code	Spreadability*(mm)
HG1	18.76±0.3
HG2	17.13±0.1
HG3	16.39±0.2
HG4	14.88±0.1
HG5	11.42±0.1

Extrudability

The extrudability of the formulated hydrogels was determined and it was found that HG1 has the highest extrudability and HG5 has got the least extrudability. The formulation HG5 with highest viscosity showed least extrudability and the formulation HG1 with least viscosity showed highest extrudability.

Table 14: Extrudability of formulated hydrogel

Formulation code	Extrudability(gm/sec)
HG1	1.78±0.1
HG2	1.65±0.2
HG3	1.43±0.1
HG4	1.26±0.1
HG5	1.17±0.2

CHARACTERIZATION AND EVALUATION OF KETOPROFEN BIGEL

Physical appearance

Physical appearance of the formulation is an important parameter for topical delivery as it affects the patient compliance. All formulations were subjected to visual appearance on the basis of transparency, colour and consistency. All formulation was found to be non transparent, off white in colour and smooth creamy consistency.

pH

The pH obtained was within topically accepted range so it would not cause any irritation.

Table 15: pH of formulated ketoprofen bigel

Formulation code	pH*
BG1	6.9±0.1
BG2	7.2±0.2
BG3	7.4±0.1
BG4	7.3±0.2
BG5	7.1±0.3

Viscosity

The viscosity of Ketoprofen bigel gradually increased from formulation BG1 to BG5. The increment was based on the concentration of organogel added to the formulation; the concentration of organogel present in the formulation was directly proportional to the viscosity of the formulation. As the formulation BG1 containing 70% organogel showed the least viscosity and the formulation BG5 containing 30% organogel showed the highest viscosity.

Table 16: Viscosity of formulated ketoprofen bigel

Formulation code	Viscosity*(cps)
BG1	6036±0.1
BG2	6120±0.1
BG3	6500±0.3
BG4	6505±0.3
BG5	6724±0.1

Spreadability

The spreadability of the formulated ketoprofen bigel was measured and it was found that the formulation BG1 has the highest spreadability and formulation BG5 has the least spreadability. Also the formulation BG1 with least viscosity showed highest spreadability and the formulation BG5 with highest viscosity showed least spreadability.

Table 17: Spreadability of formulated ketoprofen bigel

Formulation code	Spreadability*(mm)
BG1	20.21±0.2
BG2	18.23±0.1
BG3	17.78±0.7
BG4	15.33±0.2
BG5	13.21±0.1

Extrudability

The extrudability of the formulated ketoprofen bigels was determined and it was found that BG1 has the highest extrudability and BG5 has got the least extrudability. The formulation BG1 with least viscosity showed highest extrudability and the formulation BG5 with highest viscosity showed least extrudability.

Table 18: Extrudability of formulated ketoprofen bigel

Formulation code	Extrudability (gm/sec)
BG1	1.76±0.1
BG2	1.64±0.2
BG3	1.55±0.1
BG4	1.28±0.1
BG5	1.16±0.1

Gel Sol transition temperature

It was found that the formulation BG5 has the highest gel sol transition temperature and the formulation BG1 has the least gel sol transition temperature. The formulation BG1 contains 70 % organogel and the formulation BG5 contains 30 % organogel. Which implies that the gel sol transition temperature directly depends on the amount of organogel added to the formulation. As the formulation with 70 % organogel showed the highest gel sol transition temperature and the formulation with 30 % organogel showed lowest gel sol transition temperature.

Table 19: Gel Sol transition temperature of formulated ketoprofen bigel

Formulation code	Gel-Sol transition temperature(^{0}C)
BG1	44±0.1
BG2	46±0.2
BG3	49±0.1
BG4	50±0.1
BG5	51±0.2

Drug content

The drug content of the formulated ketoprofen bigel was determined. The values are reported in the Table 6.18. The values of the drug content determination ranges from 94.66±0.2% - 98.66±0.2%. From these results it was found that formulation BG5 has the highest drug content and the formulation BG1 has the lowest drug content.

Table 20: Drug content of formulated ketoprofen bigel

Formulation code	Drug content (%)
BG1	94.66±0.2
BG2	95.0±0.1
BG3	96.66±0.3
BG4	95.33±0.1
BG5	98.66±0.2

***In vitro* drug release studies**

The data of *in vitro* drug release profile of all the formulated ketoprofen bigel is given in Table 6.19. The study was carried out for 8 hrs using modified *in vitro* permeation apparatus through cellophane membrane. Formulations BG1, BG2 and BG3 showed release up to 8hrs, formulation BG1 showed 75.40% release, formulation BG2 showed 86.45% release and formulation BG3 showed 98.83% release. The formulation BG4 showed release 99.83% upto 7 hrs, formulation BG5 showed 99.83% release upto 6 hr. The percentage of organogel added to the formulation B4 and B5 was comparatively high when compared to BG1, BG2 and BG3. A significant decrease in the rate and extent of drug release was observed with increasing concentration of organogel in the formulation.

Table 21: *In vitro* drug release study of BG1- BG5

Time (hrs)	Cumulative % Drug Release of Formulation from BG1-BG5				
	BG1	BG2	BG3	BG4	BG5
0.25	17.76	16.66	16.83	18.7	25
0.5	22.50	24.81	25.21	29.38	32.76
1	34.73	36.50	34.33	37.73	44.25
2	42.60	44.25	44.56	44.41	56.83
3	48	54.83	55.58	55.18	67.21
4	55.33	67.28	67.40	67.65	74.80
5	68.51	70.30	75.55	76.43	86.28
6	69.83	76.56	83.38	87.20	99.83
7	72.16	83.86	90	99.83	-
8	75.40	86.45	98.83	-	-

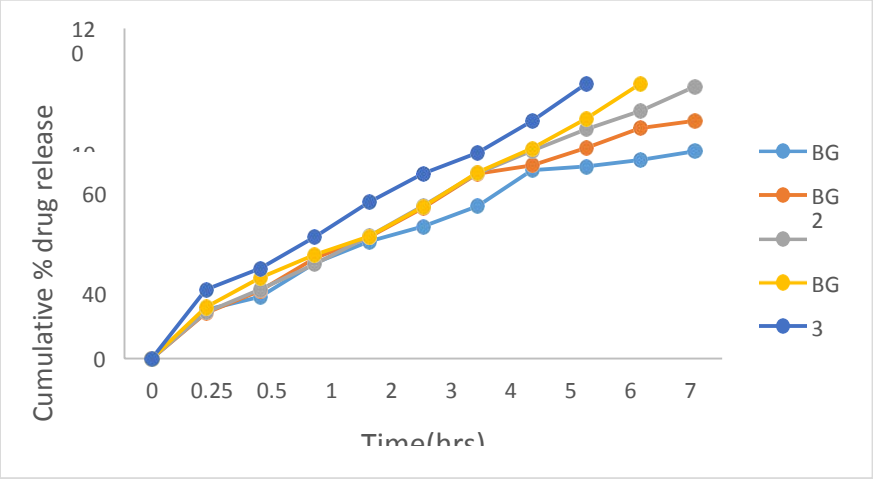

Figure 13: Cumulative % drug release of formulations from BG1-BG5

Kinetic Study

Table 22: Pharmacokinetic values of the study

Time (h)	Cumulati ve % drug released	% drug remain ing	Square root time	log cum % drug remai ning	log time	log cum % drug releas ed	% drug releas ed	Cube root of % drug remain ing (Wt)	W0 - Wt
0	0	100	0.000	2.000	0.000	0.000	100	4.642	0.000
0.25	16.83	83.17	0.500	1.920	-0.602	1.226	16.83	4.365	0.277
0.5	25.21	74.79	0.707	1.874	-0.301	1.402	8.38	4.213	0.429
1	34.33	65.67	1.000	1.817	0.000	1.536	9.12	4.034	0.608
2	44.56	55.44	1.414	1.744	0.301	1.649	10.23	3.813	0.829
3	55.58	44.42	1.732	1.648	0.477	1.745	11.02	3.542	1.100
4	67.40	32.6	2.000	1.513	0.602	1.829	11.82	3.195	1.447
5	75.55	24.45	2.236	1.388	0.699	1.878	-	2.902	1.740
6	83.38	16.62	2.449	1.221	0.778	1.921	-	2.552	2.090
7	90	10	2.646	1.000	0.845	1.954	-	2.154	2.488
8	98.83	1.17	2.828	0.068	0.903	1.995	-	1.054	3.588

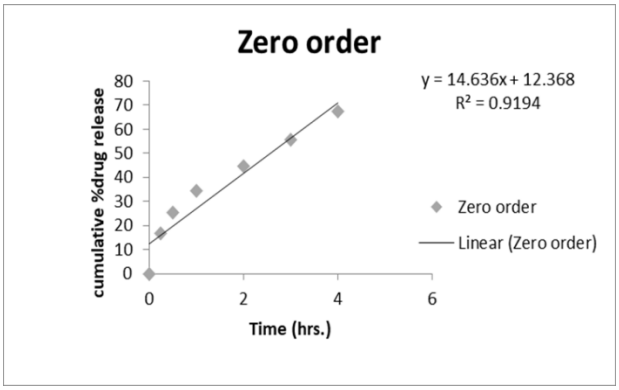

Figure 14: Zero order plot of BG3

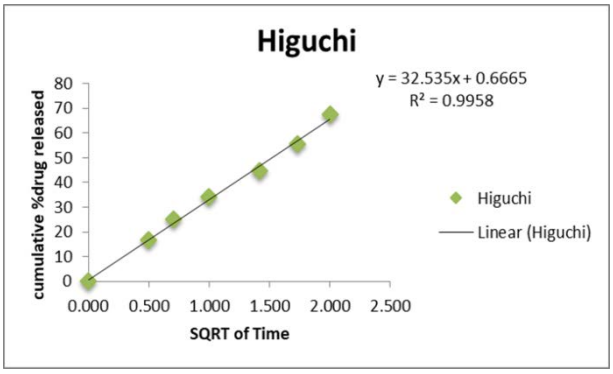

Figure 16: Higuchi plot of BG3

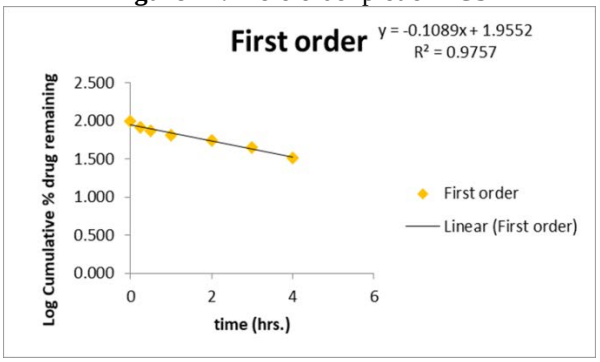

Figure 15: First order plot of BG3

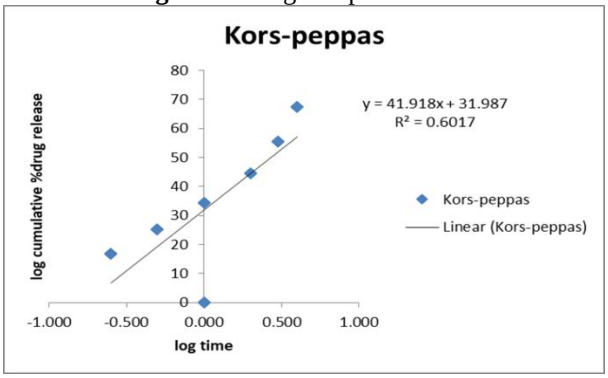

Figure 17: Kormeyer- peppas plot of BG3

Table 23: R^2 values of kinetic models

Formulation		Kinetic models		
BG3	Zero order	First order	Higuchi model	Korsmeyer-peppas model
R^2 value	0.9194	0.9757	0.9958	0.6017

The diffusion profile of optimized formulation BG3 was fitted to Zero order, First order, Higuchi model and Korsmeyer- peppas model to ascertain the kinetic modelling to drug release. It was found that the *in vitro* drug release of optimized formulation BG3 was best explained by First order as it showed the highest linearity (R^2 = 0.9757), followed by Higuchi model (R^2 = 0.9958).

***Ex vivo* drug release studies**

The *ex vivo* drug release study of the optimized formulation BG3 was carried out. The study was carried out for 8 hrs using modified *in vitro* permeation apparatus through pig ear skin membrane. The formulation BG3 showed 84.66±0.2 % drug release at the end of 8 hrs.

Table 24: *Ex vivo* drug release study of BG3

Time(hrs)	Cumulative % drug release of BG3
0.25	14.35±0.4
0.5	22.28±0.1
1	30.3±0.1
2	39±0.1
3	49.5±0.4
4	55.66±0.1
5	68.51±0.3
6	74.83±0.1
7	80.18±0.3
8	84.66±0.2

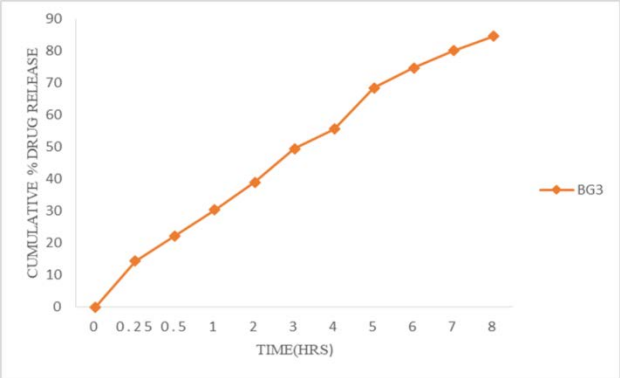

Figure 18: *Ex- vivo* cumulative % drug release of formulation BG3

CONCLUSION

In my dissertation, an attempt was made to formulate Ketoprofen Bigel. The optimised formulation from organogel and hydrogel was taken for the preparation of bigel. So it was concluded that, as per the pre- established objectives, characterizations, *in vitro* drug release studies, kinetic studies, *ex vivo* drug release studies were performed and obtained satisfactory results. The formulation BG3 had good consistency, pH of the BG3 was found to be neutral, hence it would not cause any type of irritation and exhibited maximum drug release profile hence selected as the optimized formulation. The kinetic study fitted to First order, followed by Higuchi model showing controlled release. So the Ketoprofen Bigel were found to be the most promising topical drug delivery and can be used in extended release systems.

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