EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 3
Issue: 1
156-164
Year: 2016

FORMULATION AND EVALUATION OF KETOPROFEN SOLID DISPERSION INCORPORATED TOPICAL GELS

[1]Arun Raj. R[*], [2]Elwin Jose, [3]Jyoti Harindran, [4]Sreerekha. S

[*1]Department of Pharmaceutical Sciences, Mahatma Gandhi University RIMSR, Kottayam-9, Kerala, India.
[2]Department of Pharmaceutical Sciences, Mahatma Gandhi University RIMSR, Kottayam-9, Kerala, India.
[3]Department of Pharmaceutical Sciences, Mahatma Gandhi University, Cheruvandoor Campus, Kottayam, Kerala, India.
[4]Sahodaran Ayyappan Memorial College of Education, Poothotta, Ernakulam, Kerala, India.

***Author for Correspondence: Arun Raj. R**
Department of Pharmaceutical Sciences, Mahatma Gandhi University RIMSR, Kottayam-9, Kerala, India.

Article Received on 11/11/2015 **Article Revised on 02/12/2015** **Article Accepted on 22/12/2015**

ABSTRACT
Solid dispersion technique is a promising method to improve the solubility of poorly water soluble drugs. Solid dispersions prepared with various carriers by solvent evaporation, fusion and kneading technique were effective in improving the solubility and dissolution of Ketoprofen. Ketoprofen is a potent NSAID which has analgesic and anti-inflammatory properties. Topical route for Ketoprofen was selected up to avoid GIT irritation and to maximize the drug concentration at the site of action. In the present study attempts were made to formulate and evaluate of Ketoprofen solid dispersion incorporated topical gels. Solid dispersions were prepared in various ratios using each carrier. Solubility study and dissolution study showed that as the concentration of the carrier increase, the solubility and dissolution rate of Ketoprofen increases. The particle size and surface morphology of solid dispersions were studied by SEM. IR studies showed that no chemical reaction was taken place between drug and carriers in solid dispersion. The powder X-ray diffraction study Ketoprofen - β-cyclodextrin dispersion showed that drug is present in amorphous form in solid dispersion, which could be the reason for solubility enhancement. The *in-vitro* and *ex-vivo* drug release were carried out using egg membrane and rat abdominal skin respectively in phosphate buffer pH 7.4. The *ex- vivo* release of drug from rat skin was plotted according to modes data treatment, to precisely know the mechanism involved in the drug release. The drug release mechanism from all the formulated gels was found to be predominantly diffusion controlled.

KEYWORDS: Solid dispersion, Topical gels, Ketoprofen, *In-vitro* and *ex-vivo* release studies.

1. INTRODUCTION
Solid dispersion technique is widely used to increase the intrinsic solubility and dissolution and in turns oral bioavailability of poorly water soluble compounds. Solid dispersion formulation was developed by Chiou and Riegelman. It has been used for a variety of poorly soluble drugs such as ketoprofen, tenoxicam, nifedipine, nimodipine etc. Various hydrophilic carriers such as polyethylene glycol, polyvinylpyrrolidone, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, urea, hydroxypropylmethyl cellulose phthalate, gelucires, etc. have been investigated for improvement of dissolution characteristics and bioavailability of poorly aqueous soluble drugs. Hydrophilic swellable polymers such as sodium carboxymethyl cellulose, sodium starch glycolate and pregelatinized starch are also used. In recent years, the interest in incorporating a surface active carrier into solid dispersion increased greatly and a high improvement in drug dissolution was reported.[1]

An effective topical formulation needs to provide a stable chemical environment in a suitable dispensing container in order to accommodate multiple compounds that may have different, if not incompatible, physicochemical characteristics. Once applied, a topical formulation must interact with the skin environment, which can influence the rate of the release of the compounds in order to achieve adequate skin absorption. The excipients themselves will exert additional physical effects on the skin, such as drying, occluding, or moisturizing. Research and technology have brought a better understanding of the physics, chemistry, pharmacodynamic and pharmacokinetics for drugs used to treat acne. These insights have resulted in new delivery systems that are capable of enhancing the efficacy, tolerability, and cosmetic acceptability of topical formulations.[2]

2. METERIALS AND METHODS

Materials

The following materials were used: Ketoprofen (Yarrow Chem Pvt. Ltd., Mumbai), Beta-cyclodextrin, PVP K-30, Sodium lauryl sulphate, Urea (Chemdyes Corporation, Rajkot), PEG4000, Dimethyl sulfoxide, Sodium CMC, Triethanolamine (Yarrow Chem Pvt. Ltd, Mumbai), Propylene glycol, Methanol (Nice Chemicals Pvt. Ltd, Cochi).

Methods

2.1. PREFORMULATION STUDIES

Preformulation studies were performed on the drug (API), which included melting point determination, solubility and compatibility studies.

2.2. PREPARATION OF SOLID DISPERSION

2.2.1. Kneading Method[3]

A mixture of ketoprofen and β-cyclodextrin was wetted with water: methanol (1:1v/v, 3 ml) solution, and kneaded thoroughly for 30 min in a glass mortor. The paste formed, was dried under vacuum at 60°C for a day. Pulverized, and passed through sieve no.100 and stored in a dessicator over fused calcium chloride.

2.2.2. Solvent Evaporation Method[4]

The drug and the excipients (SLS, PVP K-30, urea) in different ratios were dissolved in sufficient volume of methanol with continuous stirring. The solvent was then completely evaporated at 40 - 45˚c with continuous stirring to obtain dry granules and were pulverized and passed through sieve no.60 and stored in airtight container till further use.

2.2.3. Fusion Method[4]

Accurately weighed amount of PEG 4000 was melted in a porcelain dish at 80 - 85˚c and to this, calculated amount of ketoprofen were added with through mixing for 1-2 min followed by quick cooling. Then obtained solid dispersions are pulverized and sieve no. 60 and stored in well closed container.

2.3. EVALUATION OF SOLID DISPERSION[5, 6]

Solid dispersion formulations were evaluated and characterised by the following methods.

2.3.1. Percentage Practical yield

Percentage practical yield was calculated to know the percent yield or efficiency of any method, thus it helps in selection of appropriate method of production. SDs were collected and weighed to determine practical yield (PY) from the following equation.

$$\% \text{ Practical yield} = \frac{\text{Practical mass (Solid dispersion)}}{\text{Theoretical mass (Drug+Carrier)}} \times 100$$

2.3.2. Drug content

Solid dispersion formulations were assayed by dissolving weighed amounts (50 mg) in 50mlof phosphate buffer pH 7.4. The solution was filtered, diluted and drug content was determined UV-spectrophotometrically at 302 nm.

2.3.3. Saturation solubility study[7]

To evaluate increase in solubility of ketoprofen after solid dispersion formulation saturation solubility measurements were carried out as follows. Known excess of solid dispersion formulations was added to 10 mL of distilled water. Samples were shaken for 24 hours at room temperature in a rotary flask shaker. Samples were then filtered, suitably diluted and analyzed spectrophotometrically at 302 nm. Saturation solubility of the pure drug was also determined.

2.3.4. SEM analysis[8]

The shape and surface morphology of the solid dispersion was studied by scanning electron microscopy (SEM), JEOL JSM 6390, England. The samples were fixed on aluminum stubs with double-sided tape, gold coated sputter and examined in the microscope using an accelerating voltage of 15 kV, at a working distance of 8 mm and magnification of X500, X2000. study shows complete disappearance of crystal of drugs and confirms that drug is totally solubilized in solid dispersion system.

2.3.5. IR Spectroscopy[9]

FT-IR spectroscopy was employed to ascertain the compatibility between ketoprofen and the selected polymers using SHIMADZU A213748, JAPAN FT-IR. Potassium bromide was mixed with drug / polymer in 9:1 ratio and the spectra were taken. FT-IR spectrum of ketoprofen was compared with FT-IR spectra of ketoprofen-solid dispersion mixture.

2.3.6. X-ray Diffraction[9]

Crystallinity of the drug and the samples was determined using the Philips Analytical XRD with copper target. The conditions were: 40 kV voltages; 30 mA current; at room temperature. The samples were loaded on to the diffractometer and scanned over a range of 2^0 values form 10 to 80^0 at a scan rate of 0.05^0 /min. Generally, disappearance of characteristic peaks of drug in the solid dispersion formulation and retaining peaks of carrier material is observed. This indicates that drug get converted to amorphous form or in solubilized form in the solid dispersion system.

2.3.7. *In-vitro* drug release study[7]

The dissolution studies of solid dispersions were performed using USP dissolution apparatus type I. Dissolution study was performed in 900 mL phosphate buffer pH 7.4. The stirring speed was 50 rpm, and the temperature was maintained at 37°C±0.5°C. The samples were withdrawn at 5, 10, 15, 30, 45 and 60 minutes and were replenished with fresh dissolution medium. The samples were filtered, diluted and analyzed by UV spectrophotometer at 302nm. Dissolution studies of solid dispersions and pure drug were carried out.

2.3.8. Evaluation of pre-compression parameters of solid dispersion[10]

Flow properties such as angle of repose, bulk density, tapped density and compressibility index of solid dispersion granules, which showed better release and solubility enhancement were evaluated.

2.4. PREPARATION OF KETOPROFEN SOLID DISPERSION INCORPORATED TOPICAL GEL[11]

Gels were prepared by dispersing 2% w/w Na CMC in required quantity of water and with magnetic stirring for 3 h at 300 rpm and then neutralized with triethanolamine. Weigh accurately pure ketoprofen/ketoprofen solid dispersion and dissolved in methanol and propylene glycol. This solution was added to neutralize Na CMC with continuous stirring to form clear gel.

2.5. EVALUATION OF GELS[12]

Gels were evaluated for their Clarity, pH, Viscosity, Spreadability, Extrudability, Skin irritation test, Drug content, *In- vitro* diffusion studies and *Ex- vivo* studies by using standard procedure.

2.5.1. pH[13]

1gram of gel was accurately weighed and dispersed in 100 ml of distilled water. The pH of dispersion was measured by using digital pH meter.

2.5.2. Homogeneity

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.

2.5.3. Spreadability[14, 15]

It was determined by wooden block and glass slide apparatus**.** For the determination of spreadability excess of sample was applied in between two glass slides and was compressed to uniform thickness by placing 100 gm weight for 5 minutes. Weight (75gm) was added to pan. The time required to separate the two slides, i.e. the time in which the upper glass slide moves over the lower plates was taken as measure of spreadability (S). Spreadability was calculated by using the formula.

Spreadability, S = ML/T.

where,
S = Spreadability.
M = Weight tide to upper slide.
L = Length moved on the glass slide.
T = Time taken to separate the slide completely from each other.

2.5.4. Viscosity measurement

Brookfield digital viscometer (model DV-I+, Brookfield Engineering Laboratory, INC., USA) was used to measure the viscosity (in cps) of the prepared gel formulations. The spindle number 4 (spindle code S 64) was rotated at 15 rpm.

2.5.5. Drug content[16]

The ketoprofen gel of 50 mg was dissolved in 50 ml of pH 7.4 phosphate buffer. The volumetric flask containing gel solution was shaken for 2 hr on mechanical shaker in order to get complete solubility of drug. From this 1ml was pipetted out and made upto 10ml with pH 7.4 phosphate buffer.This solution was filtered and estimated spectrophotometerically.

2.5.6. Skin irritation test[17]

Irritation test was carried out to determine possible localised reaction of selected formula on the skin since skin safety is of prior consideration of topical gel. A single dose of selected medical formulation was applied to the left side of shaved back of male albino rabbit (1.5±0.5kg) and right side was considered as control. Control area was further divided in 2 sub areas one receiving the selected formulation unloaded with the drug and other receiving no treatment. The development of erythema was monitored daily for 6 days.

2.5.7. *In -Vitro* Diffusion Study[18]

2.5.7.1. Through Egg Membrane

Phosphate buffer of pH 7.4 was used for *in-vitro* release as a receptor medium. The pre-treated egg membrane was used in Franz diffusion cell. The gel sample was applied on the membrane and then fixed in between donor and receptor compartment of diffusion cell. The receptor compartment contained phosphate buffer of pH 7.4. The temperature of diffusion medium was thermostatically controlled at 37±1ºC by surrounding water in jacket and the medium was stirred by magnetic stirrer at 100 rpm. The sample at predetermined intervals were withdrawn and replaced by equal volume of fresh fluid. The samples withdrawn were spectrophotometrically estimated at 302 nm using phosphate buffer pH 7.4 as blank.

2.5.8. *Ex -Vivo* Diffusion Study

2.5.8.1. Through Rat Abdominal Skin

Phosphate buffer of pH 7.4 was used for *ex -vivo* release as a receptor medium. The pre treated skin of albino rat was used in Franz diffusion cell. The gel sample was applied on the skin and then fixed in between donor and receptor compartment of diffusion cell. The receptor compartment contained phosphate buffer of pH 7.4. The temperature of diffusion medium was thermostatically controlled at 37±1ºC by surrounding water in jacket and the medium was stirred by magnetic stirrer at 100 rpm. The sample at predetermined intervals were withdrawn and replaced by equal volume of fresh fluid. The samples withdrawn were spectrophotometrically estimated at 302nm using phosphate buffer pH 7.4 as a blank.

2.5.9. Kinetics of drug release[10]

To study the release kinetics of in-vitro drug release, data obtained from in-vitro release study were plotted in various kinetic models: Zero order as % drug released Vs time, First order as log % drug retained Vs time, Higuchi as % drug released Vs √time, Korsmeyer- Peppas as log

%drug released Vs log time and Hixon-Crowell as (% drug retained) $^{1/3}$ Vs time.In this by comparing the r-values obtained, the best-fit model was selected.

2.5.10. Stability studies[19]

Stability is defined as the extent, to which a product retains with in specified limits and throughout its period of strong and uses i.e. shelf life. Stability studies were carried out an optimized formulation according to international conference on Harmonization (ICH) guidelines. All the selected formulations were subjected to a stability testing for 45 days as per ICH norms at temperature 40ºC and 75% RH. All selected formulations were analyzed for the change in pH, spreadability, homogeneity or drug content by procedure stated earlier.

3. RESULTS AND DISCUSSION

3.1 PREFORMULATION STUDIES

Solubility of the drug in water, propylene glycol and methanol was examined and found to be in conformity with pharmacopoeial specifications. Table 1 explains the results of solubility studies. Ketoprofen was found to be poorly soluble in water and readily soluble in solvents like methanol and propylene glycol.

Table no.1: Solubility of drug in various solvents.

Solvent	Solubility
Water	Poorly soluble
Propylene glycol	Readily soluble
Methanol	Readily soluble

Melting point of ketoprofen was found to be 94-96^{0}C which is in conformity with the reported value. It indicates the purity of drug sample.

IR spectroscopy was carried out to check the compatibility between drug and polymers. IR spectrum of mixtures of drug and polymers –, ketoprofen and βcyclodextrin, ketoprofen and PEG 4000, ketoprofen and PVP K-30, ketoprofen and sodium CMC was recorded and compared with individual reference spectra for any spectral interference.

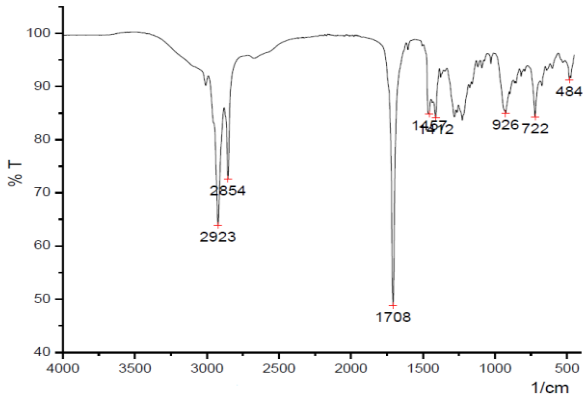


Fig.1. IR SPECTRUM OF KETOPROFEN+β-cyclodextrin.

3.2 PREPARATION OF SOLID DISPERSION

Ketoprofen solid dispersions prepared by solvent evaporation, fusion and kneading method were found to white, fine and free-flowing powders. The composition of Ketoprofen solid dispersions is given in table no.2

Tableno.2: Composition of different solid dispersion formulations.

Formulation code	Composition	Ratio	Method employed
F_1	Ketoprofen:urea	1:3	Solvent evaporation
F_2	Ketoprofen:urea	1:5	
F_3	Ketoprofen:PEG4000	1:3	Fusion
F_4	Ketoprofen:PEG4000	1:5	
F_5	Ketoprofen:SLS	1:3	Solvent evaporation
F_6	Ketoprofen:SLS	1:1	
F_7	Ketoprofen:PVP	1:3	Solvent evaporation
F_8	Ketoprofen:PVP	1:5	
F_9	Ketoprofen: β-CD	1:1	Kneading
F_{10}	Ketoprofen: β-CD	1:2	

3.3 EVALUATION OF SOLID DISPERSION

Table no. 3: Evaluation of solid dispersion formulations.

Formulation code	% Practical Yield	% drug content	Solubility (mg/mL)	Solubility enhancement ratio
Pure drug	-	-	0.6491	-
F_1	95.5	98.92	4.3370	7
F_2	96.6	96.14	5.0417	8
F_3	97.3	95.8	8.8784	14
F_4	95.8	97.12	9.0976	15
F_5	96.3	97.68	4.1961	6
F_6	97.0	97.59	4.0238	5
F_7	96.4	97.06	6.1849	9

F_8	95.9	96.62	6.6860	10
F_9	96.5	98.7	10.2721	16
F_{10}	96.0	99.7	10.6636	17

The % practical yield of all formulations was found to be between 95.5%-97.3%. The high yield of all the formulations indicates the reproducibility of solvent evaporation, kneading and fusion method techniques for the preparation of solid dispersion.

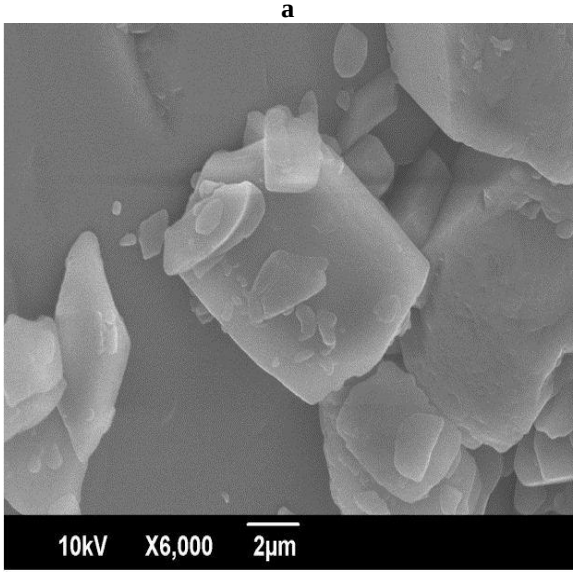
The % drug content of solid dispersions was found to be in between 95.8%-99.7%. All solid dispersion formulations showed the presence of high drug content and low standard deviations of the results. It indicates that the drug is uniformly dispersed in the powder formulation and solvent evaporation, kneading and fusion techniques is highly efficient for the preparation of uniform dispersion.

The results of saturation solubility study showed that β-cyclodextrin and PEG were efficient carriers for solubility enhancement of poorly water soluble drugs. Ketoprofen showed 14-17 fold increase in solubility from β-cyclodextrin and PEG solid dispersion formulations. As the concentration of both the carriers increased, solubility of drug was found to be increased and the solid dispersion of β-cyclodextrin with drug: carrier ratio 1:2 showed highest solubility. The results of solubility study, namely solubility of pure drug, solubility of drug in solid dispersions and solubility enhancement ratio are given in table no.3.

3.3.1. SEM analysis

The shape and surface morphology of pure drug and solid dispersions were as follows. Study shows change in crystal pattern of the drug in the solid dispersion system. These changes in crystal pattern accounts for increased solubility of solid dispersions.

a



b

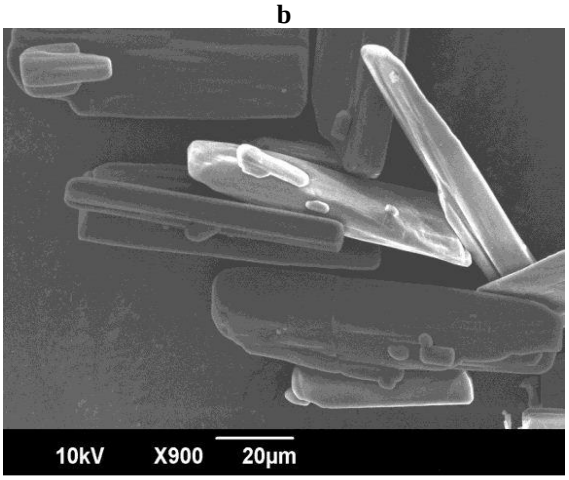
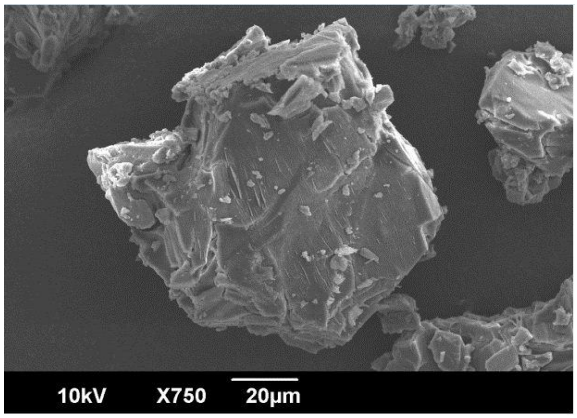


Figure. 2: SEM pictures of drug and solid dispersions – a. Ketoprofen b. PEG 4000 dispersion (F4) c. β-cyclodextrin dispersion (F10) d. PVP k-30 dispersion (F8).

3.3.2 X-ray diffraction study

c



d

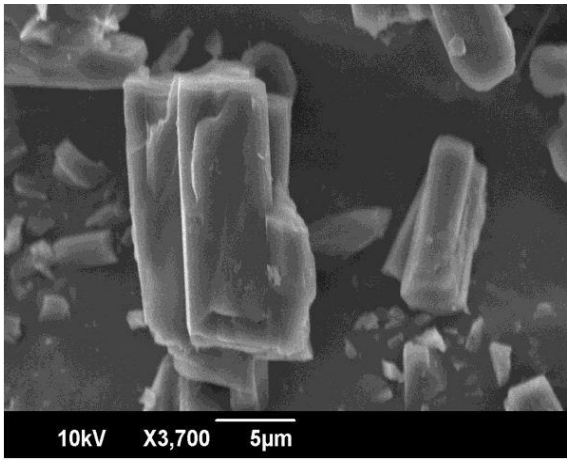


Figure. 3. Powder X-ray Diffraction pattern of pure ketoprofen.

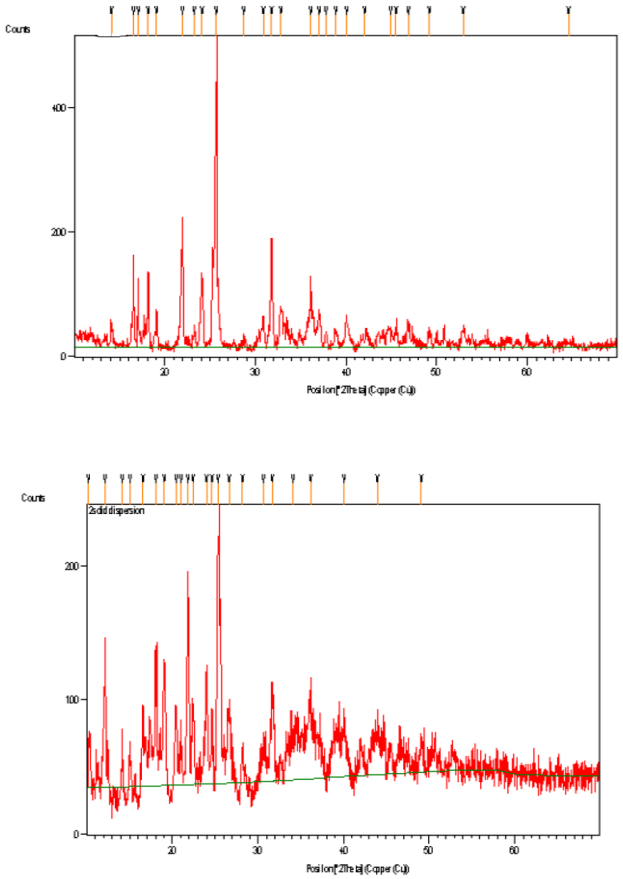


Figure. 4. Powder X-ray Diffraction pattern of solid dispersion, F10.

The diffraction angles are similar as far as both X-ray diffraction patterns are concerned. Only a decrease in reflection intensities can be pointed out for the solid dispersion sample. This suggests that crystallinity of the drug in solid dispersion could be inferior. This amorphous nature is thought to enhance the solubility of ketoprofen.

3.3.3. *In-vitro* drug release study

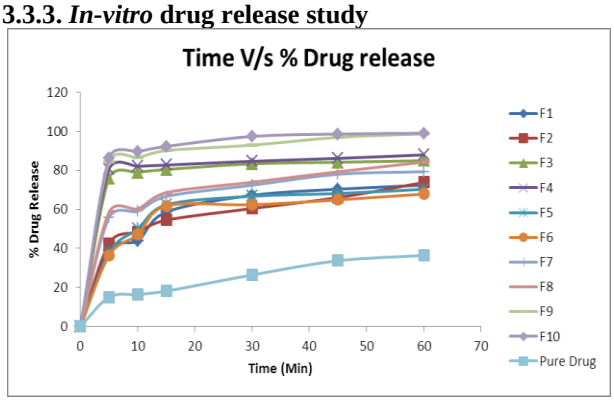


Figure. 5. *In-vitro* drug release of pure drug and F_{1-10}.

All solid dispersion formulations prepared showed faster dissolution as compared to pure drug. Cumulative % drug released at 60 minutes were 72.40%, 73.81, 84.95%, 87.93%, 70.29%, 67.25%,79.28%,84.26%,98.72%,99.01% for F1 – F10 respectively, while it was only 36.37% for pure ketoprofen. Results of dissolution study showed that as the concentration of carriers (β-cyclodextrin or PEG) increased, % drug release was also increased and beta cyclodextrin solid dispersions exhibited faster release than that of PEG dispersions.

3.3.4. Evaluation of flow properties of solid dispersion

Solid dispersion formulation, F10, which exhibited highest solubility and dissolution rate, was selected and its flow properties were evaluated to predict the suitability for formulation. The results of flow properties of various solid dispersion formulations are given in table no.4.

Table no. 4: Flow parameters of solid dispersion.

Formulation	Angle of repose	Bulk density	Tapped density	Carr's index	Hausner's ratio
F_1	34°43'	0.492g/cc	0.577g/cc	14.72%	1.23
F_2	34°75'	0.483g/cc	0.601g/cc	19.50%	1.24
F_3	35°15'	0.491g/cc	0.612g/cc	19.77%	1.24
F_4	33°88'	0.517g/cc	0.638g/cc	18.96%	1.23
F_5	34°85'	0.535g/cc	0.625g/cc	14.40%	1.16
F_6	38°09'	0.508g/cc	0.612g/cc	17.05%	1.20
F_7	38°14'	0.535g/cc	0.666g/cc	18.76%	1.24
F_8	38°65'	0.503g/cc	0.638g/cc	21.65%	1.25
F_9	33°52'	0.502g/cc	0.602g/cc	16.67%	1.20
F_{10}	31°17'	0.501g/cc	0.643g/cc	18.72%	1.23

The values of angle of repose, Carr's index and Hausner's ratio of F_{10} showed that it has suitable flow properties among various formulations.

3.4 PREPARATION OF KETOPROFEN SOLID DISPERSION INCORPORATED TOPICAL GEL

KG: ketoprofen plain gel, F1G & F2G-gels containing ketoprofen: urea in 1:3 &1:5ratio, F3G & F4G-gels containing ketoprofen: PEG in 1:3 &1:5 ratio,F5G & F6G-gels containing ketoprofen: SLS in 1:3 & 1:1 ratio, F7G & F8G-gels containing ketoprofen: PVP in 1:3 & 1:5 ratio, F9G & F10G-gels containing ketoprofen: β-cyclodextrin in 1:1 & 1:2 ratio.

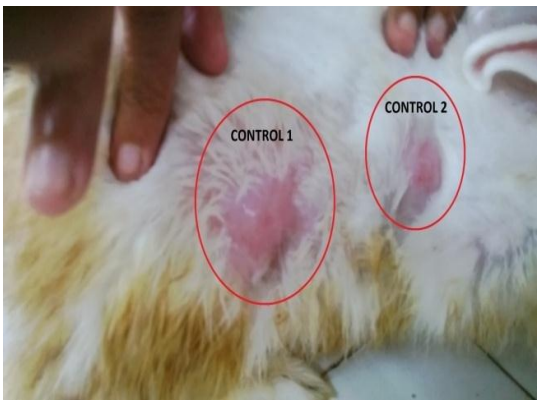
Table no.5: Formulation code of topical gel of ketoprofen solid dispersion.

Ingredients (%w/w)	Formulation Code										
	KG	F_1G	F_2G	F_3G	F_4G	F_5G	F_6G	F_7G	F_8G	F_9G	$F_{10}G$
Ketoprofen	2.5	-	-	-	-	-	-	-	-	-	-
Solid dispersion of ketoprofen	-	2.52	2.60	2.61	2.57	2.55	2.56	2.57	2.58	2.53	2.51
Dimethyl sulfoxide	5	5	5	5	5	5	5	5	5	5	5
Na CMC	2	2	2	2	2	2	2	2	2	2	2
Methanol	15	15	15	15	15	15	15	15	15	15	15
Propylene glycol	10	10	10	10	10	10	10	10	10	10	10
Methyl paraben	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Triethanolamine	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Water	q.s to 100	q.s to 100	q.s to 100	q.s to 100	q.s to 100	q.s to 100	q.s to 100	q.s to 100	q.s to 100	q.s to 100	q.s to 100

3.5 EVALUATION OF GELS

3.5.1. Skin Irritation

Absence of skin irritation in gel formulation is acceptable by patient. Skin irritation test was performed on male albino rabbit, but there was no erythema, edema or reddening of skin. All gel formulations were found to be free from irritation as shown in table no.6.Thus observations indicates acceptability of these gels for topical use.



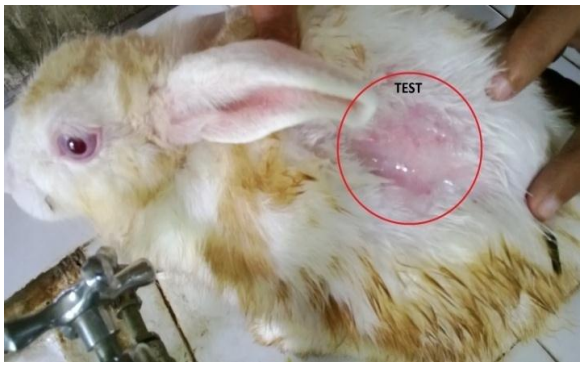


Table no.6: Values of evaluation parameters of developed gel.

Formulations	pH	Homogeneity	Viscosity(cps)	Spreadabilityg.cm/s	Skin irritation	%Drug content
F_1G	6.45	++	3687.33	11.61	-	91.17
F_2G	6.56	++	3245	11.13	-	93.34
F_3G	6.73	++	4167	17.61	-	92.22
F_4G	6.75	+++	3789.28	18.75	-	97.12
F_5G	6.81	++	3476.28	8.3	-	92.25
F_6G	6.40	++	3217.43	7.5	-	90.21
F_7G	6.43	++	4165.41	14.31	-	93.45
F_8G	6.66	+++	3655.67	12.61	-	95.27
F_9G	6.82	++	3965.87	19.08	-	94.23
$F_{10}G$	6.90	+++	4208.35	21.34	-	98.15

Note: (+) Satisfactory, (+ +) Good, (+ + +) Excellent, (-) not found.

3.5.2 *In-vitro* Diffusion Study

3.5.2.1 Through Egg Membrane

In-vitro drug release study of different gel formulations were carried out. From this we observed that ketoprofen gel with β-cyclodextrin as carrier ($F_{10}G$) showed maximum diffusion. $F_{10}G$ showed maximum flux at the end of 8 hours with an *in-vitro* drug release of 97.55%. *In-vitro* drug release from gel formulations employing various carriers like SLS, urea, PVP k-30, PEG 4000, β-cyclodextrin varies from 76.62-97.55%. The *in-vitro* drug release from various gel formulations is shown in Figure.5.

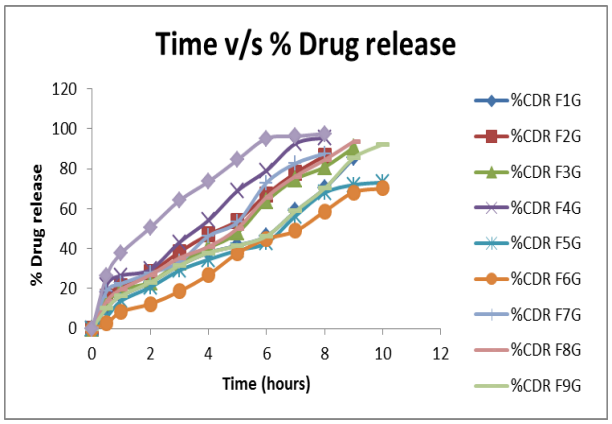


Figure 6: *In-vitro* drug release profile of F_1G-$F_{10}G$.

3.5.3. *Ex -Vivo* Diffusion Study

3.5.3.1. Through Rat Abdominal Skin

The gel formulations having maximum release were selected (F_4G, $F_8G$and $F_{10}G$) three for further release study using rat abdominal skin as diffusion barrier. The results are plotted in graphs.

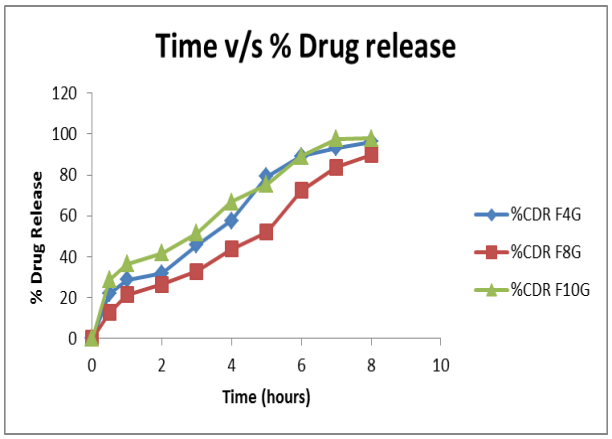


Figure 7: *Ex -vivo* drug release profile of F_4G, F_8G & $F_{10}G$.

3.5.4. Kinetics of drug release

The data were processed for regression analysis using MS-EXCEL statistical functions. Evaluation of release kinetics and application of best fit by correlation coefficient shows that the drug release follows Higuchi's equation. And their high Regression coefficient indicating the mechanism of release was diffusion controlled. From Korsemeyer-Peppas equation, release exponent was found to be less than 0.5 which means that it follows Fickian Diffusion.

3.5.5. Stability studies

According to ICH guidelines, stability studies were carried for the best formulation ($F_{10}G$) at 40ºC and 75% RH. Formulation was analyzed for homogeneity, pH, spreadability and drug content. After 45 days studies, it was revealed that there were no changes observed in homogeneity. Formulations showed slight changes in pH, but it were in acceptable limits (±0.5). Study of drug content remaining in all formulations reveals that there was no definite change observed for drug degradation as shown in table no. 7.

Table no 7: Stability Studies Data.

Formulation	pH	Spreadability(g.cm/s)	% Drug Content
$F_{10}G$	6.7	21.24	97.65

4. CONCLUSION

Solid dispersion systems have been utilized during the past four decades to increase dissolution rate and bioavailability of poorly soluble drugs. In the present study, an attempt was made to increase the *in vitro* dissolution rate of ketoprofen by solid dispersion technique. Solid dispersions were prepared in various ratios using each carrier. Solubility study and dissolution study showed that as the concentration of the carrier increase, the solubility and dissolution rate of ketoprofen increases. FT-IR spectra reveal that, all the polymers and excipients used were compatible with the drug. The particle size and surface morphology of solid dispersions were studied by SEM. The powder X-ray diffraction study ketoprofen - β-cyclodextrin dispersion showed that drug is present in amorphous form in solid dispersion, which could be the reason for solubility enhancement. All the solid dispersions were made into topical gel formulations using 2% sodium carboxy methyl cellulose as gelling agent. Utility of gels are being employed in recent past for therapeutic effectiveness of topical applied drugs. It can be concluded from the present investigation that proper selection of polymers and drug is a prerequisite for designing and developing a topical drug delivery system. Gel formulations prepared with sodium CMC showed good homogeneity, no skin irritation and good stability. The combination of Ketoprofen- sodium CMC based gel with βcyclodextrin, F10G proved to be the formula of choice, since it showed the highest percentage of drug release and good rheological properties. The formulation of choice is further ensured by kinetic release data studies and stability studies.

5. REFERENCE

1. Kalyanwat R, Patel S. Solid Dispersion: A Method For Enhancing Drug Dissolution. International Journal of Drug Formulation & Research, 2010; 1(3): 1–14.

2. JR Robinson and Lee, HL Vincent. Controlled Drug Delivery. 2nd Edn. Vol. 29, Marcel Dekker, Inc., Madison Avenue, New York, 524-526.
3. PT Tayade and PR Vavia. Inclusion complexes of ketoprofen with β -cyclodextrins: oral pharmacokinetics of ketoprofen in human. Ind J Pharm Sci., 2006; 68(2): 164-170.
4. Batra, V. Shirolkar VS, Mahaparale PR, Kasture PV and Deshpande AD. Solubility and dissolution enhancement of glipizide by solid dispersion technique. Ind J Pharma Educ Res., 2008; 42(4): 373-378.
5. Lokamatha KM, Shanta SM, N RR. Enhancement of Solubility and Dissolution Rate of Nevirapine By Solid Dispersion Technique Using Dextran: Preparation and In-vitro Evaluation. IJPRD, 2011; (12): 1–8.
6. Aejaz A, Azmail K, Sanaullah S, Mohsin AA. Formulation and In vitro evaluation of aceclofenac solid dispersion incorporated gels. Int J App Pharm., 2010; 2(1): 7-12.
7. El-Badry M, Fathy M. Enhancement of the dissolution and permeation rate of meloxicam by formulation of its freeze-dried solid dispersion in PVPK-30. Drug Dev & Ind Pharmacy., 2006; 32: 141-150.
8. Malleswara Rao V.S.N, Shyam T, Appa Rao B and Srinivasa Rao Y. Formulation and characterization of meloxicam solid dispersions. The Indian Pharmacist, 2008; 67-70.
9. Guanhao Ye, Siling Wang, Paul Wan Sia Heng, Ling Chen, ChaoWang. Development and optimization of solid dispersion containing pellets of itraconazole prepared by high shear pelletization. Int J Pharm, 2007; 337: 80-87.
10. Dash S, Murthy PN, Nath L. Kinetic modeling on drug release from controlled drug delivery systems. Acta Poloniae Pharmaceutica- Drug Research, 2010; 67(3): 217-223.
11. Dr. Barhate S. Development of Meloxicam Sodium Transdermal Gel, International Journal of Pharma Research and Development, 2010; 2(5): 1–7.
12. Dey S, Patel J.R Enhanced Percutaneous Permeability of Acyclovir By DMSO From Topical Gel Formulation, International Journal Of Pharmaceutical Sciences And Drug Research, 2009; 1(1): 13-18.
13. Sankar V, Chandrashekharan AK, Durga S, Prashanth KG and Nilani P et al. Formulation and stability evaluation of diclofenac sodium ophthalmic gels. IndJPharm Sci., 2005; 67(4): 473-476.
14. Panigrahi L, John T, Shariff A and Shobharani RH. Formulation and evaluation of
15. lincomycin HCl gels. Ind J Pharm Sci., 1997; 330-332.
16. Gupta GD and Goud RS. Release rate of tenoxicam from acrypol gels. The Indian Pharmacist, 2005; 69-75.
17. Panigrahi L, Ghosal SK, Snigdha pattnaik, Mahasana L and Barik BB. Effect of permeation enhancer on the release and permeation kinetics of Lincomycin hydrocloride gel formulation through mouse skin. Ind J Pharm Sci., 2006; 68(2): 205-211.
18. Lopez R F, Collett J H, Bently M V. Influence of cyclodextrin complexation on the in vitro permeation of skin metabolism of dexamethasone. Int J Pharm., 2000; 200: 127-132.
19. Santoyo S, Arellano A, Ygartua P, Martin C. In vitro percutaneous absorption of piroxicam through synthetic membrane and abdominal rat skin. Pharm Acta Helvetica., 1996; 71: 141-146.
20. www.ichguidelines.org.
21. Lachman L and HA Lieberman. The Theory and Practice of Industrial Pharmacy, 8th Edn. Varghese Publishing house, 2009; 534-563.
22. Jain NK and Misra. Controlled and Novel Drug Delivery, CBS Publishers and Distributors, New Delhi, 2005; 101-106.
23. Banker GS and Rhodes CT. Modern Pharmaceutics. 2nd Edn., Marcel Dekker, Madison Avenue, New York, 1990; 40: 202-205.
24. Vyas SP and Roop KK. Controlled Drug Delivery. 1st Edn. Vallabh Prakashan, 2002; 411-447.
25. Bharadwaj S & Gwalior N. Topical Gel, A Novel approach for drug delivery. Journal of Chemical, Biological and Physical Sciences, 2012; 2(2): 856–867.
26. H.C Ansel, N.G Popovich and Allen Loyd V.Pharmaceutical Dosage Forms and Drug Delivery Systems. 8th Edn., B. I. Publications Pvt. Ltd., 2005; 282-423.
27. R.M. Mehta. Pharmaceutics II, Vallabh Prakashan, 2000; 47.
28. Carter S J. Disperse system. in: Cooper and Gunn's Tutorial Pharmacy. 6th Edn. New Delhi: CBS Publishers and Distributors, 2000; 68-72.
29. Y.W. Chien. Transdermal therapeutic system. 2nd Edn., Marcel Dekker, Inc., Madison Avenue, New York, 29: 524-531.
30. Lieberman HA, Rieger MM and Banker G S. Pharmaceutical dosage form: Disperse system. 2nd Edn. New York: Marcel Dekker, 2005; 399-421.
31. Tortora GJ and Grabowski SR. Principle of Anatomy and Physiology. 10th ed. USA: Harpercollins College Publishers, 1996; 140-145.