Current Trends in Biotechnology and Pharmacy
Vol. 18(2) 1705-1712, April 2024, ISSN 0973-8916 (Print), 2230-7303 (Online)
DOI: 10.5530/ctbp.2024.2.19

Formulation and Evaluation of Piroxicam Liquid Fill Formulations

Sudhir Maddela[1*], R. R Manjula, B. Pamula Reddy, Sahithi Kodali[1], Bindu Patibandla[1], Suchitra Singavarapu[1], Raasi Maathangi[1].

[1]Department of Pharmaceutics, Nirmala College of Pharmacy, Atmakur, Mangalagiri.*Corresponding Author: sudhir.spark@gmail.com

Abstract

The present investigation includes the preparation and evaluation of liquid filling formulations of Piroxicam (PXM), a non-steroidal anti-inflammatory drug, to improve its dissolution properties. Liquid fills were prepared using various excipients like polyethylene glycol 400 (PEG 400), propylene glycol (PG), and methanol as co-solvents, poly vinyl pyrrolidone (PVP K-30) as solubilizing agent, and hydroxyl propyl methyl cellulose as gelling agent. The prepared PXM liquid fills were evaluated for appearance, recrystallization, viscosity, clarity, assay and *in vitro* drug release studies. The compatibility of PXM and excipients in liquid fills was confirmed by FTIR. DSC studies together with XRD confirmed the absence of PXM recrystallization within the liquid fills. The viscosity of the prepared liquid fills was found to be in the range of 60.9–591.7 cps. Liquid fills containing PVP K 30 gave better dissolution properties when compared to formulations without PVP K 30, and complete PXM release was observed within 60 min for all PXM liquid fills and the PXM release from liquid fills followed diffusion mechanism. The liquid fills showed 98-102% PXM content even after 6months time period indicating that the PXM was stable in liquid fill formulations.

Keywords: Piroxicam, liquid fill formulations, recrystallization, diffusion, and dissolution.

Introduction

The dissolution and bioavailability of the newly developed entities especially the BCS class II drugs remain challenged because of its poor biopharmaceutical properties. They show poor aqueous solubility at varying pH conditions throughout the gastro intestinal tract. To come across these impediments that are associated with the BCS class II drugs, the formulations scientists developed several alternative dosage forms to improve the biopharmaceutical properties of the drug substances. In this context, the liquid orals, semisolids, liquid fills (soft gels) gained importance to address the issues of bioavailability by administering the drugs through soft gelatin capsules. Initially this technology of delivering the drugs through soft gelatin capsules was widely used for the delivery of oily liquids such as cod liver oil etc (1-3). Therefore, these soft gels contain the active pharmaceutical ingredient(API) either as solution, suspension or emulsion which will enhance the absorption of API. Thus, soft gels can be considered as a best tool for the delivery of compounds with poor biopharmaceutical properties (4).

Piroxicam is a nonselective, non-steroidal anti-inflammatory drug (NSAID) which belongs to “oxicam” class and used for treating rheumatoid arthritis, osteoarthritis and other inflammatory diseases, acts by inhibiting

both COX-1 and COX-2 inhibitors (5). PXM is a drug of poor solubility and included in class II of Biopharmaceutical Drug Classification System, thereby, PXM absorbs slowly and gradually through the GIT leading to slow onset of action (6).

Various formulations have been developed for PXM like fast dissolving tablets (7), transferosme gel (6), microsponge tablet (5), solid self-micro emulsifying dispersible tablets (8), and dispersible tablets (9) to improve its solubility property. No one developed PXM liquid fills for soft gels. So, the present investigation was aimed at developing PXM liquid fills for soft gels and their evaluation to improve the biopharmaceutical properties of PXM. As these liquid fills/soft gels are used for enhanced bioavailability, many drugs are formulated in the form of soft gels. The present study deals with the formulation of piroxicam liquid fill formulations/soft gels to improve its dissolution properties.

Materials and Methods

PXM was obtained from Darwin laboratories, Vijayawada. PEG 400, PG, were purchased from Thermo Fisher Scientific India Pvt. Ltd. PVP, Sodium metabisulfite, and Methanol was obtained from Qualigens fine chemicals, Mumbai.

Methodology

Construction of calibration curve

PXM calibration curve was constructed using a series of standard solutions containing 1, 2, 3, 4, 5 µg PXM per ml. the solutions were scanned in the 200-400nm region using Shimadzu UV-1800 UV-Visible spectrophotometer. The absorbance of the standard solutions was measured at 334nm against blank (pH 1.2 buffer)

Preparation of PXM liquid fills

Liquid fill formulations were prepared by accurately weighing required quantities of PXM and other excipients as per the formulae given in Table 1. PEG 400 and PG (half of the quantity) were taken in a suitable container and then PXM was added under continuous stirring to completely dissolve the PXM. The stirring was continued till the remaining ingredients added were dissolved and a homogenous solution was obtained. Finally, the volume as adjusted with PEG 400. The prepared formulations were sonicated for 3 minutes to remove any entrapped air. The prepared formulation (equivalent to the dose of PXM) was filled in to “0” sized hard gelatin capsule with help of a syringe, the capsule body and cap were then sealed with a band to prevent the leakage of contents (10).

Table 1: Composition of PXM liquid Fills

Ingredients (mg/cap)	F1	F2	F3	F4	F5	F6	F7
PXM	20	20	20	20	20	20	20
PEG-400	60	60	50	40	40	40	-
PG	10	20	20	20	20	20	-
PVP K-30	-	-	-	-	10	20	10
HPMC	-	-	-	-	-	-	60
SBS	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Methanol	10	-	10	20	10	-	10
Total weight	100	100	100	100	100	100	100

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Evaluation of PXM liquid filling formulations

The PXM liquid fills were evaluated for the following properties

Morphological properties

Properties such as homogeneity, color, transparency, and appearance of PXM liquid fills are tested visually against a black background. All the formulations were stored at room temperature (25 ± 3°C) with relative humidity of approximately 65 ± 5% and were tested periodically every month for a period 6 months (9). The results are given in Tables 2 and shown in Fig: 1

SEM studies

The PXM liquid fills were further investigated for recrystallization by scanning electron microscopy (SEM-JOEL, JSM-840A, Japan). The samples to be examined were mounted on the SEM sample slab using a double-sided adhesive tape. The samples mounted were coated with gold ($200A^0$) under reduced pressure (0.001 torr) for 5min to improve the conductivity using an Ion sputtering device (JOEL, JFC-1100E, Japan) (10).

DSC analysis

Thermograms of PXM and selected PXM liquid fills were recorded using Differential Scanning Calorimeter (Schimadzu, DSC-60, Japan). Samples weighing 5mg were sealed in aluminum pans and heated to 400ºC at a rate of 10ºC per minute. Samples were heated from 50-400ºC (10).

X- RD analysis

XRD studies of PXM and selected PXM liquid fills were performed using X-Ray Diffractometer (Schimadzu, XRD-7000, Japan) with Cu-Kα radiation at 40kV and 30mA. X-Ray diffraction patterns were collected over 2θ range of 10-40º at a scan rate of 4º per minute (10).

FTIR analysis

Samples were analyzed using ATR-FTIR spectrometer (Bruker, Germany). ATR spectra were measured over the wave number range of 4000-500 cm^{-1} at a resolution of 1.0 cm^{-1}. The powder or liquid fill sample is simply placed onto the ATR crystal and the sample spectrum is collected. FTIR spectra of PXM and mixtures (PXM + excipients in 1:1 ratio) were shown in Fig 5.

Drug content

Accurate amount of PXM liquid fills equivalent to dose of PXM was taken in a 10mL volumetric flask and dissolved in 5mL of methanol and the volume was made up with distilled water. Samples were suitably diluted with pH 1.2 buffer and the absorbance was measured at 334nm. The estimations were carried out in triplicate (10).

Variation of mass:

Mass variation among the different batches of PXM liquid fills was calculated by measuring the mass of each capsule equivalent to PXM dose. The estimations were carried in triplicate.

Rheological studies

The viscosity was measured using Brookfield DV-II + PRO viscometer of cup and bob type. The formulation was taken into the cup of viscometer and measured using spindle CP52 at 10 rpm. The viscosity measurements were made in triplicate using fresh samples each time (10).

***In vitro* drug release studies**

In vitro drug release studies were conducted using 900 mL of pH 1.2 buffer as a dissolution medium using USP type II (paddle) apparatus (DISSO 8000, LAB INDIA). A temperature of 37°C and a rotation speed of 50 rpm were maintained. PXM Liquid fills were filled into hard gelatin capsule (size 0) and dissolution studies were performed. As the capsule tends to float in the dissolution medium, sinkers were used. A 5 mL sample was withdrawn at predetermined

time intervals over a period of 1 hr and then replaced with the same volume of fresh dissolution medium. The filtered samples were suitably diluted and analyzed at 334 nm using UV-visible Elico SL150 spectrophotometer. Dissolution experiments were conducted in triplicate (10).

Results and Discussion

Preparation of Liquid fills

In the present investigation the liquid fills were prepared for easy administration and quick release of medicament which is also a commercially scalable technique. Initially, placebo liquid fills were prepared with different polymers like HPMC E3, Sodium CMC, Sodium Alginate, PG, and PEG-400 and observed for gel forming capacity and appearance. The liquid fills prepared with PG, PEG and HPMC E3 were transparent and showed good flow ability, whereas, the liquid fills prepared with sodium CMC, sodium alginate were turbid and are highly viscous. So, PG, PEG, and HPMC E3 were selected for further development of liquid fills. The liquid fills prepared with PEG and PG were stable, homogenous and clear even after the addition of PXM. Whereas the liquid fills with HPMC E3 were turbid after the addition of PXM. Hence, further the liquid fills were prepared with PEG and PG only. The PXM liquid fills were prepared as per the formulae shown in Table 1.

Evaluation of PXM liquid fills

Morphological properties

The prepared PXM liquid fills were visually tested for homogeneity, transparency, color and smoothness. Soft gels with PEG-400 and PG showed no change in properties even at the end of 6-month time and no crystallization of PXM was observed. The results were given in Table 3. Soft gels formulated with HPMC E3 were opaque which may be due to recrystallization of PXM in liquid fills. The results were shown in Fig1.

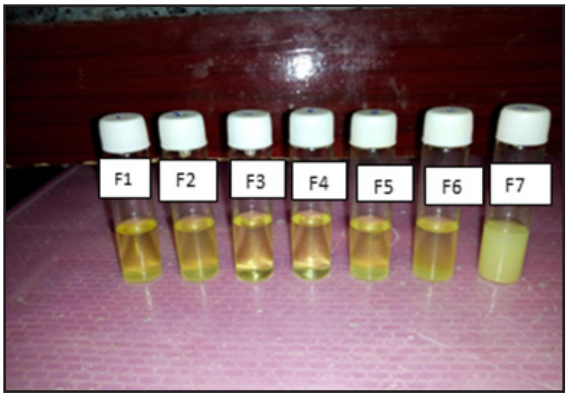

Fig 1: Morphological Properties of PXM liquid Fill Formulations (0-6 months)

SEM analysis:

The PXM liquid fills were further investigated for PXM recrystallization in liquid fills by SEM analysis. The scanning electron micrographs of PXM and selected PXM liquid fills were shown in Fig 2. The visualized SEM micrographs revealed that the liquid fills were relatively clear and maintained the transparency, this may be due to molecular dispersion of PXM in liquid fills.

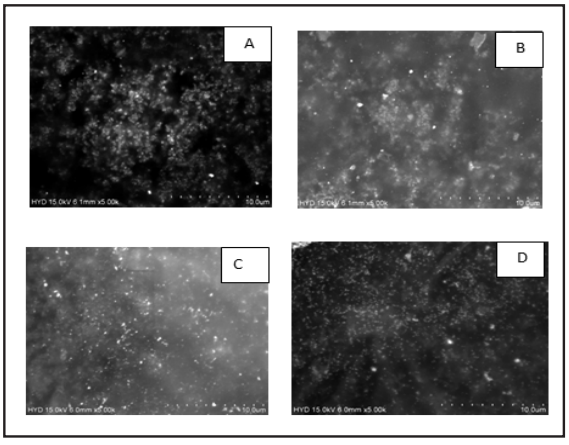

Fig 2: SEM micrographs of PXM Liquid Fills (A) PXM, (B) F4, (C) F6, (D) F7

DSC analysis:

DSC thermograms obtained for PXM and PXM soft gels were shown in Fig3. PXM showed melting endotherm at 200 ºC. PXM soft

gels showed no, or weak peaks compared to PXM. This may be due to molecular dispersion of PXM within soft gels. Overall DSC curves indicate that there is no interaction observed between PXM and excipients.

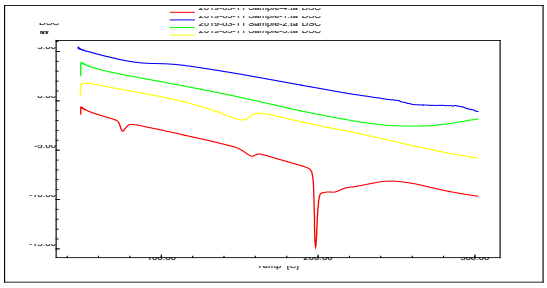

Fig 3: DSC Thermograms of (-----) PXM, (-----) F1, (-----) F4, (-----) F6

X-RD analysis

Selected PXM soft gels were subjected to X-RD studies to investigate the crystallographic properties of PXM in soft gels. PXM showed characteristic peaks at 16.54, 19.82, 24.50, 27.32 and 38.07 2θ. The X-ray diffractograms of the PXM liquid fills showed weak or no signals when compared to the characteristic peaks of pure PXM. This may be due to molecular dispersion of PXM within the soft gels. Overall, together with DSC data the X-RD results clearly indicate that the PXM was not in crystalline state in liquid fills. The X-ray diffractograms of PXM and selected PXM liquid fills were shown in are shown in Fig 4.

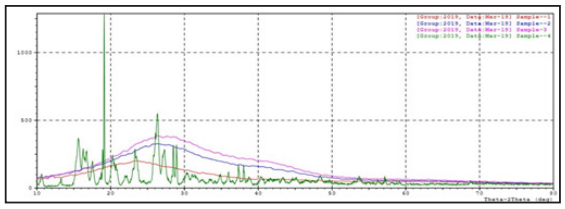

Fig 4: X-RD diffractograms of (----) PXM, (-----) F1, (-----) F4, (----) F6

FTIR analysis

The PXM showed characteristic peaks at 1681cm^{-1}(ketone C=O stretching), 668cm^{-1} (C=Cl due to Halogen compound), 2311cm^{-1}(N-H amino acid stretching). These characteristic peaks of PXM were all retained in the soft gels. These results were given in Table7 and indicate that there is no interaction between PXM & excipients in soft gels. The FTIR spectra of PXM alone and in combination with excipients were shown in Fig 5.

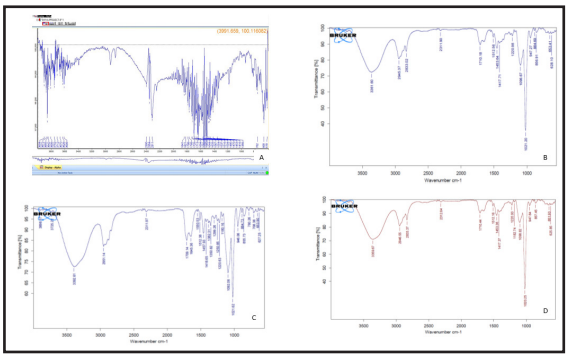

Fig 5: FTIR spectra of (A) PXM, (B) PXM+PEG-400, (C) PXM+PG, (D) PXM+PEG 400+PG+PVP K30

Drug content

The PXM content within the liquid fills were found to be in the range of 18.70 to 20.11mg. The results were given in Table 2. The results indicated a good uniformity of PXM within the liquid fill, and overall good solubilization of PXM in liquid fills was observed. The liquid fills formulated with PVP gave superior PXM content compared to liquid fills without PVP.

Variation of mass

The mass of PXM liquid fills equivalent to 20mg dose of PXM from three different batches were recorded on electronic balance (shimadzu-ATX224) and the results are shown in Table 2. Same mass of the soft gels was obtained with the three batches of the soft gels indicating the reproducibility of the soft gel preparation method and formulation.

Rheological studies

The viscosity of the PXM liquid fills was measured using Brookfield viscometer with spindle 52 was reported in Table 2. From the data obtained it is observed that the consistency of the liquid fills was dependent upon

the concentration of PEG-400. Even though the PEG is selected as co-solvent the high consistency nature of PEG enhanced the viscosity of the prepared liquid fills, hence increased PEG concentration lead to high viscous liquid fills. In fact, the PG has decreased the consistency of the prepared liquid fills, thereby, a 2.05-fold decrease in viscosity was observed F 6 compared to F1. A significant increase in viscosity was observed in liquid fill containing HPMC (F7) compared to other formulations which may be due to the influence of gelling agent (HPMC). However, the addition of PVP to the formulation showed a negligible effect on the viscosity of liquid fill formulations.

Table 2: Evaluation Parameters for PXM Liquid Fill Formulations

Formulation	Variation of mass± SD	Viscosity± SD	Drug content ± SD
F1	100.85 ± 0.204	140.8±0.10	19.01 ± 0.02
F2	100.86 ± 0.287	126.9±0.02	19.43 ± 0.06
F3	100.21 ± 0.085	105.8±0.06	19.08 ± 0.06
F4	100.13 ± 0.170	94.5±0.10	19.39 ± 0.02
F5	100.13 ± 0.047	82.6±0.01	19.04 ± 0.03
F6	100.45 ± 0.108	68.5±0.05	20.11 ± 0.05
F7	100.79 ± 0.152	275.5±0.01	18.70 ± 0.01

In vitro drug release studies

In the present investigation, dissolution of PXM soft gels was carried out using USP Type-II Dissolution Rate Testing Apparatus and 900mL of pH 1.2 buffer was used as dissolution medium. The *in vitro* dissolution profiles of PXM liquid fills were shown in Fig3. The cumulative percent of PXM released at the end of 5 min for F1, F2, is 15.50 ± 2.4, and 35.44 ± 1.9 respectively. A 2.2 folds increase in PXM release was observed in formulation F2 compared to formulation F1 indicating that increased concentration of PG significantly attributed the co-solvency effect and thereby superior dissolution rates were obtained with increased concentration of PG which can be. The comparative dissolution profile of PXM liquid fill F1 and F2 were shown in Fig 6(A). The cumulative percent of PXM release from F2, and F3 is 35.44 ± 1.9, 48.46 ± 3.4 respectively at the end of 5 minutes. A 1.36-fold increase in PXM release was observed in formulation F3 compared to F2, indicating that a decrease in concentration of PEG enhanced the PXM release from liquid fills which might be due to decrease in consistency of the liquid fills due to lesser concentration of PEG compared to F2. The comparative dissolution profile of PXM liquid fill F2 and F3 were shown in Fig 6(B). Further trails were carried out to study the effect of PVP K30 on PXM release rates from the liquid fills. The cumulative percent of PXM released at the end of 5 minutes from F4, F5, and F6 is 53.86 ± 3.7, 77.84 ± 2.4, and 90.15 ± 2.6 respectively. A 1.44-, and 1.67-fold increase in PXM release was observed in F5, and F6 compared to F4 indicating that PVP K30 enhanced the PXM release from liquid fills. The comparative dissolution profile of PXM liquid fills F4, F5, and F6 were shown in Fig 6(C). The cumulative percent of PXM released from F7 is found to be 12.26± 0.5 at the end of 5 minutes, indicating that HPMC significantly lower the PXM release from liquid fills because of its high consistency.

The viscosity of the liquid fills also showed significant effect on PXM release form liquid fills. The liquid fills of high consistency (F1, F2, F3, and F7) showed slow PXM release whereas the liquid fills with low consistency (F4, F5, and F6) showed faster PXM release. Overall, the formulations F5 and F6 containing PVP K30 showed significant superior PXM release compared to F4 without PVP K30.

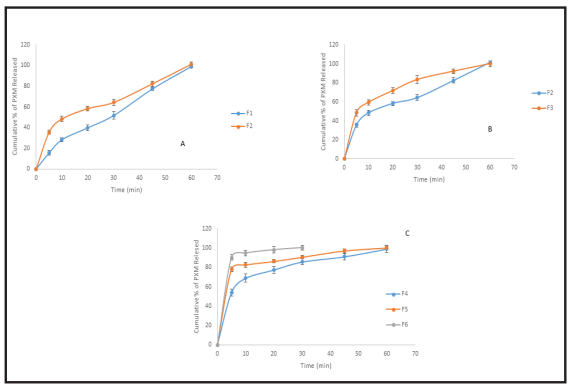

Fig 6: Comparative *in vitro* drug release profile of PXM Liquid Fills

Drug release kinetics

To better understand the release profiles obtained with PXM liquid fills, the drug release data obtained at different time points was fitted in to different kinetic models such as First order (11), and Higuchi model (12).

The first order release rate constant 'k' (sec^{-1}) values and correlation coefficient (R^2) values calculated from dissolution data (0-60 min) of PXM liquid fills. The 'k' values for F1to F7 were found to be 0.13, 0.18, 0.27, 0.45, 0.61, 0.7, and 0.12 respectively. A 1.35, and 1.55 fF5, and F6 compared to F4. The liquid fills containing PVP K30 significantly showed higher K values compared to liquid fills without PVP K30.

The Higuchi square root model of all soft gels showed higher correlation coefficient values (0.76-0.98) indicating diffusion as release mechanism.

Conclusion

The dissolution properties of PXM can be enhanced by using co-solvents (PG and PEG), and solubilizing agent PVP K30 by formulating as liquid fills. The liquid fills with PEG showed more consistency compared to PG. all the liquid fills showed good physico-chemical properties and were stable till the end of 6months. Overall the liquid fills with PVP K30 showed superior dissolution rates compared to liquid fills without PVP K30.

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