PREPARATION AND CHARACTERIZATION OF SOLID DISPERSION USEFUL IN MAKING SUBLINGUAL TABLETS OF PIROXICAM

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ABSTRACT

This study aimed to investigate the usage of solid dispersion (SD) to enhance the dissolution rate of the poorly soluble drug piroxicam for sublingual formulation. Poloxamer grade 407 (Kolliphor® P-407), a commercially available polymer, was chosen, and various solid dispersions with different weight ratios of piroxicam and Poloxamer were prepared using the hot melt method. Compatibility tests using FTIR spectroscopy, DSC, and XRD were conducted to assess any chemical or physical interactions between the drug and polymer. *In vitro* dissolution tests were performed on the solid dispersions. The results of the FTIR spectroscopy study indicated no chemical interaction between the drug and the polymer. Similarly, the DSC and XRD analyses showed no physical interaction between the drug and the polymer. The maximum cumulative percentage release of the pure drug and the solid dispersion at 15 minutes were 40.90±1.83% and 99.56±3.25%, respectively. Based on these findings, it was concluded that the solid dispersion with a ratio of 2:1 (Drug: Poloxamer-407) showed a noteworthy upsurge in the dissolution rate in comparison to the pure drug.

Keywords: Piroxicam, Poloxamer-407, Solid dispersion, FTIR, DSC, dissolution enhancement.

INTRODUCTION

Piroxicam is a non-steroidal anti-inflammatory drug (NSAID) that is poorly water soluble and extremely permeable and is used to treat osteoarthritis and rheumatoid arthritis[1,2]. Under the Bio-pharmaceutics Classification System (BCS), it is classed as a Class-II drug. It is given as fast-dissolving tablets for pain management and has a quick onset of analgesic effect, but it undergoes a lot of hepatic first-pass metabolism[3]. This drug's dissolving rate is the rate-controlling stage that restricts preparation methodologies to produce various dosage forms[4]. Piroxicam has been studied in a variety of dosage forms, including microcapsules, solid dispersion niosomes, nanoparticles, nano-emulgel, micro-emulsions, microspheres and transdermal delivery[5-10]. Through escaping first-pass hepatic metabolism as well as enzymatic breakdown in the gastrointestinal tract (GIT), the sublingual route can achieve high bioavailability. Sublingual drug delivery is a method of drug administration in which pharmacological compounds injected under the mouth are absorbed directly through blood vessels[11]. Small regions for absorption, short residence duration, possible discomfort and unintended ingesting of the dose form are all disadvantages of this administration route[12].

Poloxamer, a non-ionic triblock copolymer, composed mainly of polyoxyethylene units, is FDA-approved and listed in the Inactive Ingredient Guide[13,14]. It forms micelles, enhances solubility, prevents drug crystallization and thickens solutions. It remains liquid at room temperature but gels at body temperature, aiding in drug delivery and solubility enhancement. Its surfactant properties promote drug dispersion and site adherence, making it beneficial for controlled release applications[13-15]. Because of their temperature-dependent gelation efficiency, mucoadhesive formulations like the poloxamer-based formulation can significantly enhance the residence period at the mucosal location[16]. Swelling and erosion of the polymer matrix are

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frequently used to modulate drug release from micellar gel formulations[17].

When given sublingually, piroxicam effectively decreased postoperative discomfort, trismus and edema in volunteers undergoing third molar extraction, according to clinical research results[18,19]. Since the solid dispersion for piroxicam formed with poloxamer 407 is a novel method, it can help with faster dissolving, absorption and patient compliance. This study aimed to create solid dispersions of piroxicam utilizing the transition property of poloxamer.

MATERIALS AND METHODS

Poloxamer (Kolliphor® P407) was kindly gifted by Chemdyes Corporation, Rajkot, Gujarat. Propylene glycol, microcrystalline cellulose (PH 102), and mannitol were obtained from Astron Chemicals, Ahmedabad, Gujarat. Piroxicam was purchased from Alkem Laboratories Ankleshwar, Gujarat. Crospovidone was obtained from Ozone International, Mumbai, Maharashtra. Kyron T-314 was gifted by Corel Pharma, Ahmedabad, Gujarat.

Preparation of solid dispersion by hot melt method

Piroxicam was combined with poloxamer 407 in various ratios (1:1, 1:2, 1:3, and 2:1), and with PEG 4000 in ratios of 1:2 and 1:3. The mixtures were melted in a glass dish in a 70°C water bath while stirring continuously until homogeneous. They were then rapidly solidified in an ice bath with vigorous stirring. The resulting solid was crushed, pulverized, and sifted through a #60 sieve[20].

CHARACTERIZATION OF SOLID DISPERSION

FTIR analysis

FTIR spectrum of the final optimized batch was carried out. The dispersion was mixed separately with potassium bromide. The sample was scanned over a wave number range of 4000cm^{-1} to 400cm^{-1} in an FTIR instrument (IR, 8400-S, Shimadzu, Japan)[21].

Differential scanning calorimetry (DSC)

The DSC thermogram was obtained using a Shimadzu DSC 60 instrument. Samples weighing approximately 2-5 mg were heated from 5°C to 300°C at a rate of 10°C/min under a nitrogen stream flowing at 10 mL/min[21].

X-ray diffraction (XRD)

Powder XRD patterns were obtained using PANalytical Expert Pro equipment with Cu-Kα radiation (45 kV, 40 mA, 40°C). Samples were scanned from 5.99 to 39.99° in 0.0008° increments at a rate of 8.2550 seconds per step, utilizing a zero-background sample holder[22].

In vitro dissolution study of solid dispersion

Dissolution testing was conducted using USP apparatus II with each solid dispersion equivalent to 20mg of piroxicam in 250 mL of pH 6.8 simulated salivary fluids for 1 h. The paddle rotation speed was set at 50 rpm at a temperature of 37±0.5 °C. Aliquots (5mL each) were withdrawn at specified intervals over 1 h, and drug content analysis was performed using a Shimadzu UV-2450 double-beam UV spectrophotometer[23].

RESULTS AND DISCUSSION

Preparation of solid dispersion by hot melt method

The solid dispersion of piroxicam was prepared by the hot melt method. The composition of SD is shown in Table I.

Table I: Composition of solid dispersion preparation

SD ratio		Piroxicam (mg)	Poloxamer 407 (mg)	PEG 4000 (mg)
Piroxicam: poloxamer 407	2:1	100	50	-
	1:1	100	100	-
	1:2	100	200	-
	1:3	100	300	-
Piroxicam: PEG 4000	1:2	100	-	200
	1:3	100	-	300

FTIR ANALYSIS

Characteristic absorption peaks due to specific groups present in piroxicam are shown in Figs. 1-3 and Table II. These characteristic peaks are also found in the solid dispersion. So there was no interaction between drug and carrier.

Thermal analysis (DSC Study)

The DSC thermograms of piroxicam, poloxamer-407, and an SD with a 2:1 ratio prepared via the hot melt method were recorded using a Shimadzu DSC 60 calorimeter (Figs. 4-6). The thermogram of plain piroxicam exhibited a single endothermic peak at 202.83°C, representing drug melting. Poloxamer-407 showed melting endotherm at 57.90 °C. In the SD thermogram, individual peaks of

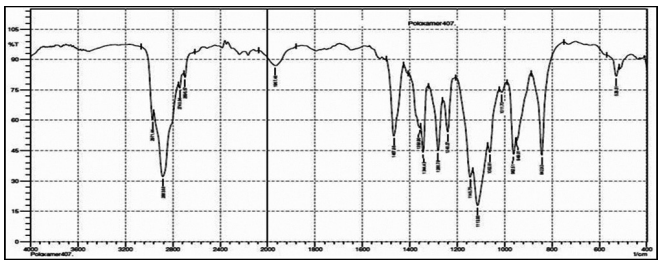

Fig. 1: FTIR spectrum of piroxicam

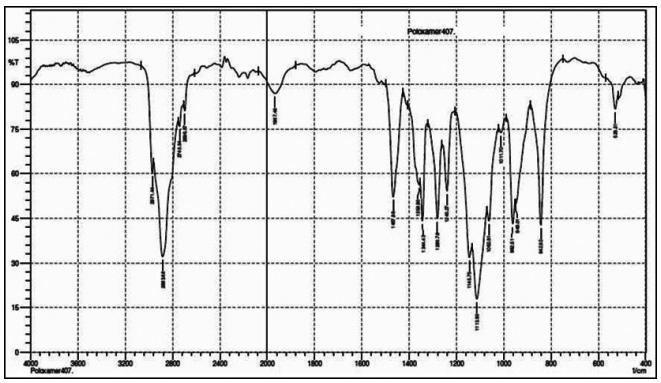

Fig. 2: FTIR spectrum of poloxamer-407

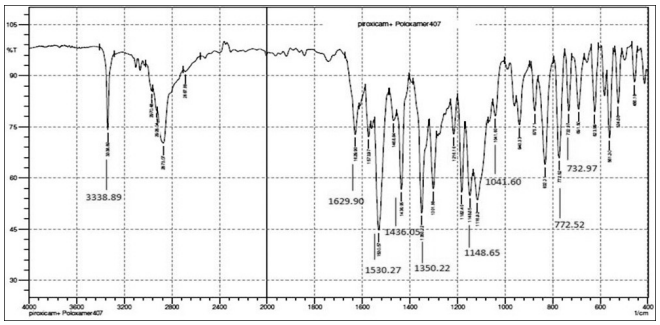

Fig. 3: FTIR spectrum of final optimized batch (solid dispersion 2:1)

piroxicam and poloxamer-407 were observed, indicating no physical interaction between the drug and polymer[24].

X-ray diffraction (XRD)

Powder XRD patterns for piroxicam, poloxamer 407, and the solid dispersion were obtained using a PANalytical Expert Pro instrument with Cu-Kα radiation at 45 kV and 40 mA, maintaining a temperature of 40°C (Fig. 7-9). X-ray diffractograms of piroxicam and poloxamer 407 and solid dispersion were used to investigate the drug's polymorphism. The diffraction pattern of piroxicam in solid dispersion has shown various intense peaks as in plain drug diffractogram; so no physical interaction was found between drug and polymer, and the drug was molecularly dispersed in a polymer matrix[24].

Table II: Peak of drug and final optimized batch of solid dispersion

Functional group	Piroxicam wave number cm^{-1}	Solid dispersion (2:1) ratio wave number cm^{-1}
-NH stretching	3336.96	3338.89
-CONH stretching	1624.12	1629.90
Secondary amide band	1527.67	1530.57
$-CH_3$ (asymmetrical); Ar-C=C- stretching	1438.94	1436.05
$-CH_3$ (symmetrical)	1354.07	1350.22
$-SO_2$-NH	1149.61, 1037.74	1148.65, 1041.60
Ortho di-substituted phenyl	771.55, 736.83	772.52, 732.97

In vitro dissolution study of solid dispersion

Dissolution studies are crucial for assessing solid dispersions (SD). Formulations exhibiting maximum uniformity and higher amorphous drug content typically demonstrate enhanced dissolution. Pure API showed the slowest dissolution rate, while formulations with higher polymer content exhibited the fastest release

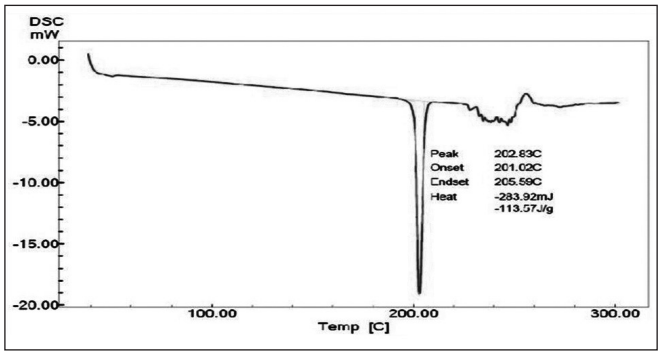

Fig. 4: DSC thermogram of piroxicam

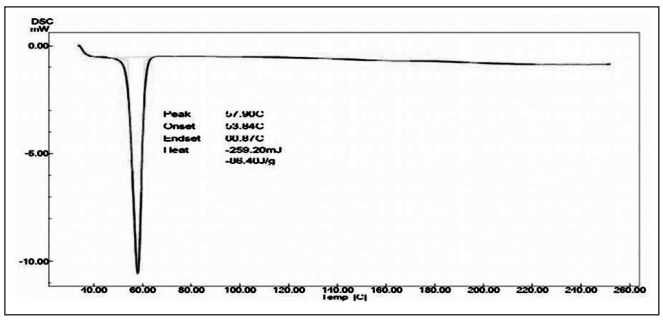

Fig. 5: DSC thermogram of poloxamer 407

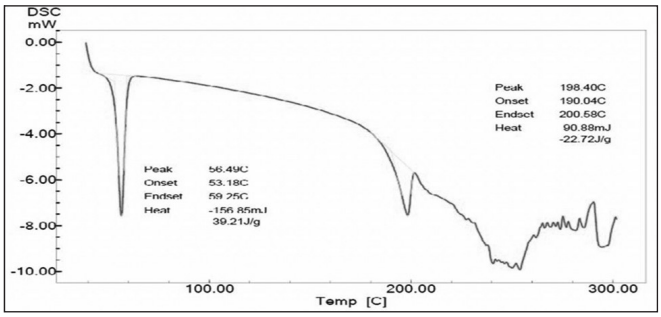

Fig. 6: DSC thermogram of solid dispersion of piroxicam with poloxamer 407(2:1 ratio)

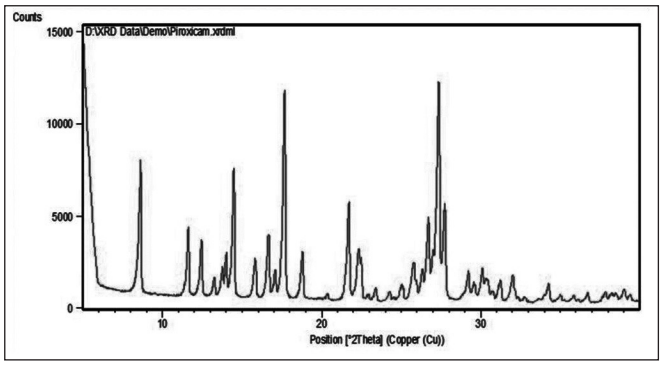

Fig. 7: XRD graph of piroxicam drug

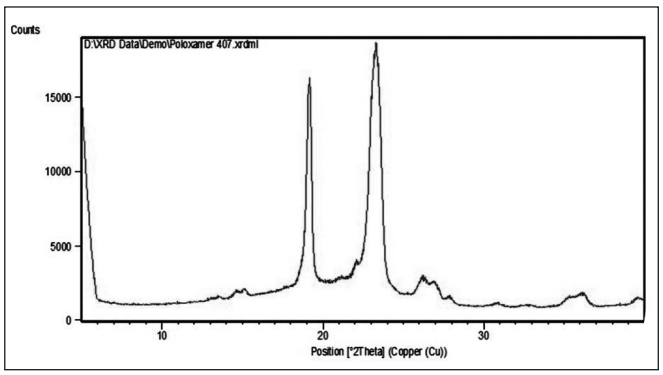

Fig. 8: XRD graph of poloxamer 407

rates. Poloxamer 407, being water-soluble, enhances SD solubility, leading to increased dissolution. Physical mixtures showed higher dissolution compared to pure API but lower than SD due to the carrier's dissolution effect. In the fusion technique, molecular dispersion occurs at the melting point, but upon quenching cooling, heterogeneous and recrystallized products may form. Dissolution profiles in pH 6.8 fluids revealed a significantly higher release rate at a piroxicam:poloxamer 407 ratio of 2:1. The maximum cumulative release percentages at 15 minutes were 40.90±1.83% for pure drug and 99.56±3.25% for SD (Fig. 10)[25].

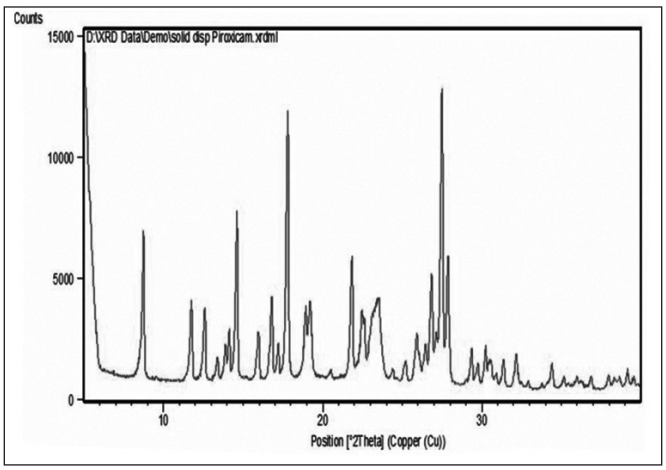

Fig. 9: XRD of solid dispersion of piroxicam with poloxamer 407 (2:1 ratio)

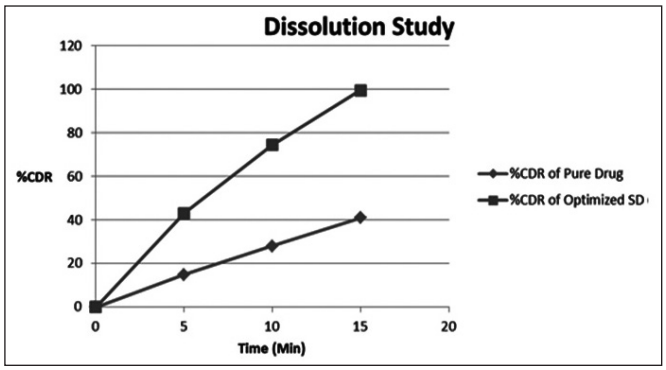

Fig. 10: Cumulative % drug release from pure piroxicam and 2:1 ratio of solid dispersion of piroxicam

The SD of piroxicam was prepared using the hot melt method with different ratios of poloxamer 407 and PEG 4000. FTIR analysis revealed no interaction between the drug and carriers. DSC thermograms showed distinct peaks for piroxicam and poloxamer 407, indicating no physical interaction. X-ray diffraction patterns suggested molecular dispersion of piroxicam in the polymer matrix. Dissolution studies demonstrated enhanced release rates with higher polymer content, attributed to increased solubility facilitated by poloxamer 407. The 2:1 ratio of piroxicam to poloxamer 407 exhibited the highest release rate. Overall, the SD showed superior dissolution compared to pure drugs, making it a promising formulation strategy for improving drug solubility and release.

CONCLUSION

In summary, based on the aforementioned research, it can be inferred that poloxamer 407 has the potential to improve the dissolution of piroxicam, a drug that is poorly soluble in water. Poloxamer 407 plays a crucial

part in increasing the solubility and dissolution of the drug. The highest amount of drug released within 15 minutes was 40.90±1.83% for the pure drug, while for the drug formulated with Poloxamer 407, it was 99.56±3.25%. Among the various carriers tested, poloxamer 407 demonstrated superior capabilities in enhancing solubility and dissolution.

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