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Design, Formulation and Evaluation of Piroxicam Capsules Prepared by Solid Dispersion Technique

Shady A. Swidan[1], Hassan M. Ghonaim[2*], Mamdouh M. Ghorab[2] and Ahmed M. Samy[1]

[1]Department of Pharmaceutics, Faculty of Pharmacy and Pharmaceutical Industries, Sinai University, El-Arish, North Sinai, Egypt.
[2]Department of Pharmaceutics, Faculty of Pharmacy, Suez Canal University, Ismailia, Egypt.

Authors' contributions

This work was carried out in collaboration between all authors. Author SAS designed the study, wrote the protocol, and wrote the first draft of the manuscript. Author HMG managed the analyses of the study, managed the literature searches and overall revision and submission. Author MMG and AMS supervised the entire research. All authors read and approved the final manuscript.

Research Article

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ABSTRACT

Objective: To improve the dissolution of poorly soluble Piroxicam (PRXM) by solid dispersion technique using water soluble carriers with or without the addition of sodium lauryl sulphate (SLS) as surfactant.
Methods and Materials: Solid dispersions of Piroxicam were prepared using different polymers such as polyethylene glycol (PEG 4000 and PEG 6000) polyvinylpyrrolidone (PVP K30 and PVP K90) without or with addition of 2% of (SLS). Solid dispersions were formulated in drug polymer ratios 1:1, 1:2, and 1:4, each ratio without or with 2% SLS using solvent evaporation method. The prepared formulae were assayed for drug content, production yield and stability properties. Dissolution profiles were done in phosphate buffer pH 7.4 and the in vitro release was evaluated according to the % released after 20, 30, 45 and 60 minutes. An accelerated stability study was done over 3 months at 40° and 60ºC and with relative humidity (RH) 75%.
Results and Discussion: All of the formulated solid dispersions displayed better dissolution profiles as compared to the pure drug. Formulae containing 2% SLS displayed

**Corresponding author: Email: hassan_ghonaim@pharm.suez.edu.eg;*

better in vitro release results compared to formulae prepared without SLS. The degradation of PRXM was slow, indicating the chemical stability of PRXM in all prepared formulae.
Conclusion: A formula containing PRXM to PEG 4000 in the ratio 1:1 with 2% SLS was ranked first and gave the best results among prepared formulae.

Keywords: Piroxicam; PEG; PVP; solid dispersion; dissolution enhancement; solvent evaporation; accelerated stability.

1. INTRODUCTION

Recently more than 40% new chemical entities (NCEs) developed in pharmaceutical industry are practically insoluble in water. Formulation of poorly soluble compounds for oral delivery now presents one of the interesting challenges to formulation scientists in the pharmaceutical industry [1]. Piroxicam is a well-established non-steroidal anti-inflammatory drug (NSAID) exhibiting anti-inflammatory, analgesic and antipyretic properties. It is widely used in rheumatic diseases because of its potent anti-inflammatory properties and long half-life (about 50 h) offering the convenience of a once-daily administration [2]. According to the Biopharmaceutical Classification System PRXM is regarded as a class II compound characterized by low solubility. Drug release is a crucial and a limiting step for oral drug bioavailability, particularly for drugs with low gastrointestinal solubility and high permeability. By improving the drug release profile of these drugs, it is possible to enhance their bioavailability and reduce side effects [3-7].

The term 'solid dispersion' has been utilized to describe a family of dosage forms whereby the drug is dispersed in a biologically inert matrix, usually with a view to enhancing oral bioavailability [8]. Another definition mentioned by Vasconcelos et al. (2007) was 'molecular mixtures of poorly soluble drugs in hydrophilic carriers [9].

Solid dispersion was first characterized by Sekiguchi and Obi [10], they noted that the formulation of eutectic mixtures improve the rate of drug release and, consequently, the bioavailability of poorly water soluble drugs. In the late sixties, a second generation of solid dispersions appeared, containing amorphous carriers instead of crystalline ones [11]. Recently, it has been shown that the dissolution profile can be improved if the carrier has surface activity or self-emulsifying properties, therefore third generation solid dispersions appeared. These contain a surfactant carrier, or a mixture of amorphous polymers and surfactants as carriers [9].

Several methods are used in solid dispersion preparations, such as hot melt extrusion, supercritical fluid method and solvent evaporation method.

The solvent evaporation method consists of the solubilization of the drug and carrier in a volatile solvent that is later evaporated [12-14]. In this method, the thermal decomposition of drugs or carriers can be prevented, since organic solvent evaporation occurs at low temperature [15].

A basic process of preparing solid dispersions of this type consists of dissolving the drug and the polymeric carrier in a common solvent, such as ethanol [16,17], chloroform [18,19] or a mixture of ethanol and dichloromethane. Normally, the resulting films are pulverized and milled [5,13,16,17].

Several carrier systems have been used in the preparation of fast release solid dispersions. Polyethylene glycols (PEG) are polymers of ethylene oxide, with a molecular weight (MW) usually falling in the range 200-300,000.Their solubility in water is generally good, but decrease with MW. A particular advantage of PEGs is that they also have good solubility in many organic solvents.

Additional attractive feature of the PEGs include their ability to solubilize some compounds and also to improve compound wettability [20].

PEGs of MW 4000-6000 are the most frequently used for enhancement of solubility of poorly water soluble drugs because in this MW range the water solubility is still very high. If a PEG with too low MW is used, this can lead to a product with a sticky consistency that is difficult to formulate into a pharmaceutically acceptable product [21].

Polymerization of vinylpyrrolidone leads to polyvinylpyrrolidone (PVP) of molecular weights ranging from 2500 to 3000000. Due to their good solubility in a wide variety of organic solvents, they are particularly suitable for the preparation of solid dispersions by the solvent method. Similarly to the PEGs, PVPs have good water solubility and can improve the wettability of the dispersed compound in many cases [22].

Increased dissolution rates and extent of absorption were found in rabbits following administration of the sulphathiazole-urea eutectic mixtures [10]. Poloxamer 407 increased the aqueous solubility of piroxicam by about 11-fold at the concentration of 22.5% w/w [23]. For ursodeoxycholic acid the release rate from urea dispersions prepared by the hot melt method was faster than from other carriers studied, including PEG 6000 [24]. PVP was used to enhance the dissolution rate of a number of drugs such as 5-lipoxygenase inhibitor SB210661 and benidipine HCl [25]. Dissolution of prednisolone has been enhanced by PEG fusion dispersions [26]. Jachowicz and Czech [27] formulated piroxicam solid dispersions containing hydroxypropyl methylcellulose acetate succinate (HPMCAS) as a carrier for ocular delivery.

Solid dispersion technique was used also to formulate sustained release dosage forms, Aburahma and coworkers [28] formulated lornoxicam using solid dispersion technique with Eudragit RS as a sustained release matrix.

The aim of this work was to prepare PRXM by a solid dispersion technique using PEG (4000, 6000) and PVP (K30, K90) in order to enhance its solubility, in vitro release and hence its bioavailability. It also aimed to make comparative study showing the effect of addition of SLS as surfactant. Accelerated stability testing is made to evaluate the effect of the solid dispersion using different polymers on the physical stability of PRXM.

2. MATERIALS AND METHODS

2.1 Materials

PRXM kindly donated by Medical Union Pharmaceuticals, Abu Sultan, Ismailia, (Egypt). PEG 4000 and PEG 6000, PureLab, Madison, (USA). PVP K30, Winlab Leicestershire, (United Kingdom). PVP K90, Alpha Chemica, Mumbai, (India). Methanol, PureLab, Madison, (USA). SLS, Al Nasr Pharmaceutical Chemical Co., (Egypt). Sodium dihydrogen phosphate,

PureLab, Madison, (USA). Chloroform, Labscan Ltd, Dublin (Ireland). Sodium hydroxide, OxfordLab, Mumbai, (India), Sodium chloride, Al Nasr Pharmaceutical Chemical Co., (Egypt).

2.2 Equipment

Hitachi, U-2900 U.V spectrophotometer (Japan). USP dissolution tester, six cup model, Apparatus I, Erwika. Apparatebau GmbH, (Germany). Sieve 200 µm, and sieve 125 µm, USA standard test sieve, ASTME-11. specification, Gilson company, 1NC 1-800-444-1508 (USA). Electric balance, SARTORIUS, TE2145, 4 decimal, (Germany). Shimadzu 435vU-O4 IR spectrophotometer, (Japan). Oven, Binder GmbH Bergster. 14 D-78532 Tuttlingen (Germany). pH meter, JENWAY designed and manufactured in the EU by Barlworld Scientific Ltd, Dunnlow, Essex, CM6 3LB, (United Kingdom).

2.3 Methods

2.3.1 Preparation of PRXM solid dispersion by the solvent evaporation method

The calculated amount of PRXM and the employed polymers (PEG 4000, PEG 6000, PVP K30 or PVP K90) in different drug-polymer ratios (1:1, 1:2 and 1:4) besides SLS as surfactant (0 or 2%) are weighed and mixed together in a porcelain dish. Twenty four different formulae were prepared by the solvent evaporation method. The mixture was dissolved in the least amount of chloroform as a common solvent [19]. Then the solvent was evaporated in oven at temperature 50ºC till complete evaporation.

The solid dispersions prepared were pulverized in a mortar and sieved. The fraction of the powder that passed through 200 µm and retained on a 125 µm sieve was collected, stored in a desiccator and used for further investigations.

2.3.2 The production yield

The production yields of the prepared PRXM solid dispersions were studied, since it measures the actual weight of the prepared solid dispersion (drug + polymer + the surfactant). This value was calculated by dividing the actual yield of the solid dispersion produced (before sieving) over the theoretical yield and multiplied by 100.

2.3.3 The drug content

A specific amount of the prepared PRXM solid dispersion equivalent to 5 mg was dissolved in 50 ml ethanol to produce a stock solution (100 µg /ml). One ml of the stock solution was withdrawn and completed to 10 ml using methanol. The concentration of this solution was (10 µg /ml). The solution was assayed spectrophotometrically at λ353 nm for calculating the PRXM content [29]. The polymers did not show any interference with the absorbance of the drug at this wave length [30].

2.3.4 Fourier Transform Infrared Spectroscopy (FTIR)

The samples of PRXM powder, PEG 4000, PEG6000, PVP K30 and PVP k90 separately, 1:1 solid dispersion of each substance with PRXM and 1:1 physical mixture of PRXM and SLS were previously ground and mixed thoroughly with spectral grade potassium bromide.

The KBr discs were prepared by compressing the powders. The scanning range was from 4000-400 cm^{-1} [31,32]. IR spectra were obtained using a Shimadzu 435 U-O4 IR spectrometer. This was carried out by The National Center of Research, Cairo, Egypt.

2.3.5 In vitro release study of PRXM capsule

The dissolution behavior of the 24 formulae of PRXM solid dispersions were compared with the pure PRXM powder. The dissolution studies were performed by USP dissolution tester, apparatus I (basket method).

An accurately weighed amount of prepared solid dispersion equivalent to 10 mg of PRXM was placed in a hard gelatin capsule. Each capsule is placed in a basket containing 900 ml of phosphate buffer pH 7.4 [33,34]. The basket is rotated at 100 rpm. The temperature of the in vitro release medium was maintained at 37ºC± 0.5ºC. Each sample was run in triplicate in which 5 milliliters aliquot were withdrawn at 5 ,10, 15, 20, 30, 45, 60 and 75 minutes then replaced by 5 ml of fresh pre-warmed phosphate buffer pH 7.4. Samples were analyzed spectrophotometrically at λ353 nm using phosphate buffer (pH7.4) as a blank. The cumulative percentage released is calculated.

The experiments were conducted in triplicates and the mean ± SD was calculated using Microsoft office excel, 2010.

The data of the in vitro release of pure PRXM and PRXM solid dispersion capsules were treated by different kinetic orders to explain the mechanism for each formula. So, the studied formulations of PRXM were subjected to zero, first and Higuchi's diffusion model [35]. The kinetic parameters and correlation coefficient were calculated for the in vitro release of PRXM [36].

2.3.6 Stability studies of PRXM capsule

Stability studies on solid dispersion formulae were performed by keeping the samples at (40ºC) and (60ºC) with relative humidity of 75% which was obtained by using saturated solution of sodium chloride [37].

These studies were performed for a period of 3 months. The samples were withdrawn at regular time intervals of 2, 4, 6, 8, 10 and 12 weeks [38].

These samples were analyzed for drug content by UV spectrophotometric method at the previously determined λ_{max}. The amount of drug decomposed and the amount remaining (un-decomposed drug) at each time interval were calculated. The experiments were conducted in triplicate and the mean ±SD was calculated using Microsoft office excel 2010.

The data from stability studies of PRXM solid dispersion were treated by different kinetic orders to explain the mechanism for each formula. The studied formulae of PRXM were subjected to zero, first and second order kinetics. The kinetic treatments, kinetic parameters, and correlation coefficients were calculated for the shelf stability of PRXM [30].

The best kinetic order for the degradation of PRXM formula can be calculated from the highest values of the obtained correlation coefficients. It was possible from the calculated experimental accelerated stability testing to calculate the specific reaction rate constants corresponding to the two elevated temperatures. This was calculated using some form of

Arrhenius equation and substituting the experimentally established specific rate constants at two elevated temperatures, the energy of activation can be determined as follows:

$$\text{Log } (K_2/K_1) = (Ea/2.303\ R) \times [(T_2-T_1) / (T_2T_1)]$$

Where: $\mathbf{K_1}$ is the specific reaction rate constant at temperature T_1.
$\mathbf{K_2}$ is the specific reaction rate constant at temperature T_2.
Ea is the energy of activation.
R is the gas constant (1.987 Cal. / degree mole).
$\mathbf{T_1}$ and $\mathbf{T_2}$ are absolute temperatures.

In this way, it will be possible to predict the decomposition reaction rate constant at room temperature, $K_{20,}$ and by a second substitution in the Arrhenius equation using the determined activation energy and one of the elevated temperature rate constants.

Knowing K_{20}, it was possible to calculate the half-life, as well as, the time after which the dosage forms lost 10% of their drug content. This later value, t_{90}, is the time through which the dosage forms would remain complying with official requirements of drug content.

3. RESULTS AND DISCUSSIONS

3.1 Preparation of PRXM by Solid Dispersion Using the Solvent-evaporation Method

Twenty four different formulae of PRXM solid dispersions were prepared using procedures previously mentioned in the methodology, see Table 1.

The solid dispersions formed varied in their physical properties according to the type of polymer used and the proportions of drug to polymer. Formulae containing PVP were more viscous, sticky and more difficult to be sieved than formulae containing PEG polymer.

PVP K90 formulae were more sticky and elastic than PVP K30. The lower the ratio of the drug to the polymer, the more elastic the solid dispersion will be. This was consistent with the results of Tantishaiyakul et al. which stated that, PRXM: PVP K90 ratio lower than 1:4 were not investigated due to the stickiness of the preparations with the increasing amount of the polymer. Tantishaiyakul et al., prepared solid dispersion of PRXM and PVP K90 in a similar concentration and procedure to the present work [39].

The same results were obtained when PRXM-Cimitidine solid dispersion prepared by solvent evaporation technique [40]. Also, PRXM-polymer (Eudragit RS100 or Eudragit RL100) solid dispersions were prepared by the solvent method [23].

Table 1. The suggested formulae of PRXM solid dispersions

Formula	Polymer used	Drug : Polymer ratio	Percentage of SLS
1 PEG4000	PEG 4000	1:1	----
1 PEG4000(S)		1:1	2%
2 PEG4000		1:2	----
2 PEG4000(S)		1:2	2%
4 PEG4000		1:4	----
4 PEG4000(S)		1:4	2%
1 PEG6000	PEG 6000	1:1	----
1 PEG6000(S)		1:1	2%
2 PEG6000		1:2	----
2 PEG6000(S)		1:2	2%
4 PEG6000		1:4	----
4 PEG6000(S)		1:4	2%
1 PVP-K30	PVP K30	1:1	----
1 PVP-K30(S)		1:1	2%
2 PVP-K30		1:2	----
2 PVP-K30(S)		1:2	2%
4 PVP-K30		1:4	----
4 PVP-K30(S)		1:4	2%
1 PVP-K90	PVP K90	1:1	----
1 PVP-K90(S)		1:1	2%
2 PVP-K90		1:2	----
2 PVP-K90(S)		1:2	2%
4 PVP-K90		1:4	----
4 PVP-K90(S)		1:4	2%

PVP K 25 was used for preparing Refocoxib solid dispersions [19], while Shavi and coworkers prepared the solid dispersions by dissolving the mixture of Gliclazide and the PVP K 30 at the weight ratios of 1:0.5, 1:0.75 and 1:1 w/w, with the aid of a minimal volume of mixture of methanol and acetone solvent system (1:1 v/v)[41].

3.2 The Production Yield

The values of the production yield of the 24 formulae of PRXM solid dispersion before sieving were ranging from 96.4 to 99.8 %. Satisfactory reproducibility of results when repeating the preparations was observed. Table 2 shows the production yield of the prepared formulae. The obtained results were found to be in good agreement with the specifications of the official pharmacopeias [42,43].

Formula 1 PEG4000 gave the highest value (99.8%) for the production yield while formula 21 2 PVP-K90 gave the lowest value (96.4%).

The rank order for the production yield of PRXM solid dispersions using different polymers and different drug-polymer ratios can be arranged, in descending order, as follows: 1 PEG4000, 2 PEG4000(S), 1 PEG4000(S) , 4 PEG4000(S) , 2 PEG6000(S) , 4 PEG6000(S) , 4 PEG4000, 4 PEG6000, 1 PEG6000, 2 PVP-K30, 2 PEG6000, 1 PVP-K90(S), 2 PEG4000, 1 PVP-K90, 2 PVP-K30(S), 1 PEG6000(S), 4 PVP-K30, 1 PVP-K30(S), 4 PVP-K30(S),2 PVP-K90(S), 4 PVP-K90(S), 1 PVP-K30, 4 PVP-K90, 2 PVP-K90.

Table 2. Production yields and drug contents of the prepared PRXM solid dispersions

Formula	Production yield % (PY)		Actual drug content (mg) (DC)		Rank order (PY+DC)
	Value	Rank	Value	Rank	
1 PEG4000	99.8% ± 0.02	1	102.0% ± 0.89	7	1
1 PEG4000(S)	99.5% ± 0.15	3	103.3% ± 1.10	10	3
2 PEG4000	98.8% ± 0.08	13	102.9% ± 0.91	9	11
2 PEG4000(S)	99.7% ± 0.13	2	104.7% ± 0.71	16	8
4 PEG4000	99.3% ± 0.17	7	105.1% ± 1.10	19	15
4 PEG4000(S)	99.5% ± 0.14	4	103.9% ± 1.70	13	6
1 PEG6000	99.2% ± 0.24	9	100.1% ± 0.80	1	2
1 PEG6000(S)	98.2% ± 0.16	16	100.9% ± 2.06	6	11
2 PEG6000	98.9% ± 0.0	11	99.7% ± 0.36	2	3
2 PEG6000(S)	99.5% ± 0.35	5	103.7% ± 0.15	12	6
4 PEG6000	99.3% ± 0.12	8	103.5% ± 0.42	11	9
4 PEG6000(S)	99.4% ± 0.04	6	105.4% ± 0.81	21	17
1 PVP-K30	96.9% ± 0.21	22	99.4% ± 1.48	4	15
1 PVP-K30(S)	97.6% ± 0.21	18	100.8% ± 1.10	5	13
2 PVP-K30	99.0% ± 0.25	10	96.1% ± 0.90	13	13
2 PVP-K30(S)	98.4% ± 0.47	15	95.0% ± 0.90	18	19
4 PVP-K30	97.9% ± 0.12	17	95.4% ± 0.57	15	18
4 PVP-K30(S)	97.6% ± 0.14	19	92.4% ± 1.27	23	22
1 PVP-K90	98.5% ± 0.25	14	98.0% ± 1.79	7	10
1 PVP-K90(S)	98.9% ± 0.09	12	99.7% ± 1.36	2	5
2 PVP-K90	96.4% ± 0.36	24	95.1% ± 1.82	17	20
2 PVP-K90(S)	97.5% ± 0.46	20	86.3% ± 2.15	24	23
4 PVP-K90	96.8% ± 0.23	23	93.1% ± 0.55	22	24
4 PVP-K90(S)	97.1% ± 0.19	21	94.8% ± 0.90	20	20

Tantishaiyakul and co-workers studied the solid dispersions formed between PRXM and the PVP K17 or PVP K90 and found that the higher the viscosity of the polymer the lowest the production yields calculated [39].

Pignatello et al., found that the production yield of 1:2 PRXM-Eudragit RS100 solid dispersion was 58% and 1:5 PRXM solid dispersion was 73%. The low results of the obtained production yield were due to difficulty in collecting all the solid material from the flask after ethanol evaporation [30].

3.3 The Drug Content

As shown in Table 2 the drug content of different formulae ranged from 86.3% to 105.4%. The obtained results were found to be in good agreement with the specifications of the official pharmacopeias [42,43].

The amount of PRXM in the solid dispersion formulae can be arranged in descending manner as follows: 1 PEG4000 > 1 PEG6000 > 1 PEG4000(S) > 2 PEG6000 > 1 PVP-K90(S) > 4 PEG4000(S) > 2 PEG6000(S) > 2 PEG4000(S) > 4 PEG6000 > 1 PVP-K90 > 2 PEG4000 > 1 PEG6000(S) > 1 PVP-K30(S) > 2 PVP-K30 > 4 PEG4000 > 1 PVP-K30 > 4

PEG6000(S) > 4 PVP-K30 > 2 PVP-K30(S) > 2 PVP-K90 > 4 PVP-K90(S) > 4 PVP-K30(S) > 2 PVP-K90(S) > 4 PVP-K90.

Pignatello and his colleagues found that the drug content of 1:2 PRXM-Eudragit RS100 solid dispersion was 75.7% and 1:5 was 100% [30].

Table 2 also represented the rank order of PRXM solid dispersions concerning both the production yields and the drug contents. Formula 1 PEG4000 was found to be the best formulation of PRXM solid dispersion followed by formula 1 PEG6000.

3.4 Fourier Transform Infrared Spectroscopy (FTIR)

Piroxicam polymorphic forms have been reported to have different FTIR. For needle forms Piroxicam shows the band of N-H and enolic O-H at 3385 cm^{-1}, while for cubic forms at 3330 cm^{-1} [44].

In the present work, the O-H stretching vibration of PRXM appeared at 3455 cm^{-1} as a broad peak while N-H appeared at 3336 cm^{-1}.PRXM structure might exist at a mixture of Keto, enol or zwitterionic forms. Fig. 1 shows the structure of PRXM in its three different forms.

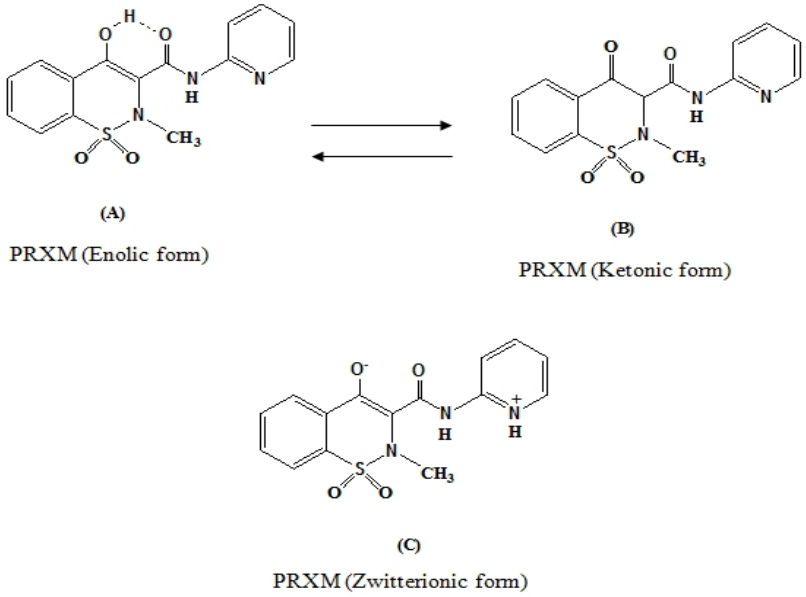

Fig. 1. Structure of PRXM in three different forms a) enolic form b) ketonic form c) zwitterionic form

The appearance of a medium peak of conjugated ketone of the FTIR spectrum at 1629 cm^{-1} indicates that PRXM preferred to be present in the enol form (A) which is stabilized by six membered intermolecular hydrogen bonding or in zwitterionic form (C). FTIR also revealed the presence of weak peaks at 3100 and 3062 cm^{-1} for υ C=C in addition to the sp3 C-H at 2926 and 2852 cm^{-1} for (υ CH3). Fig. 2 illustrate the FTIR spectra of the drug and the four polymers separetely and the solid dispersion of the PRXM and each compound separately.It also shows the spectrum of SLS and the 1:1 mixture of PRXM and SLS.

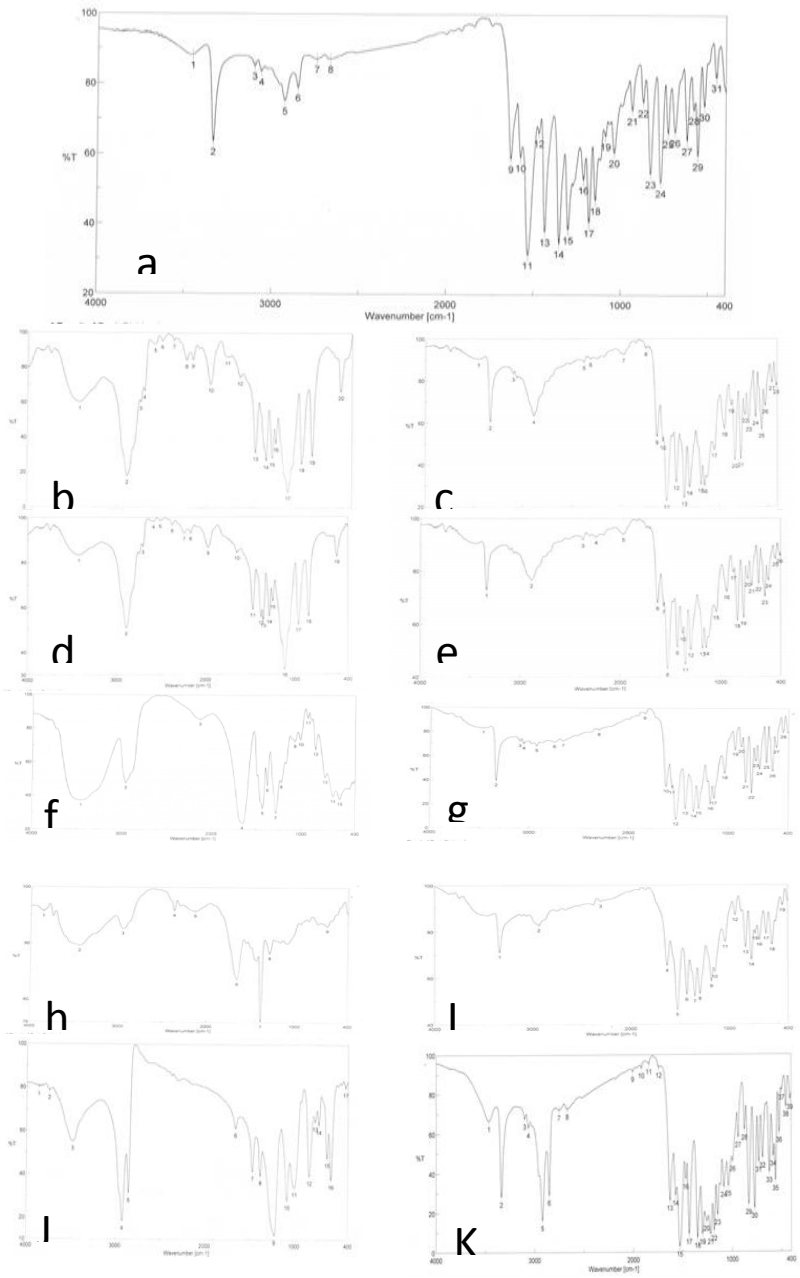

Fig. 2. IR spectra of: a- PRXM; b- PEG4000; c- PRXM+ PEG4000 mixture; d- PEG6000; e- PRXM+ PEG4000 mixture; f- PVP K30; g- PRXM+ PVP K30 mixture; h- PVP K90; I- PRXM+ PVP K90 mixture; J- SLS; K- PRXM+ SLS mixture

FTIR spectra of PEG 4000 and PEG 6000 showed broad O-H peaks at about 3420 cm^{-1}, sp3 C-H stretching peaks at 2887 cm^{-1} in addition to the sharp ether linkage (C-O-C) at 1110 cm^{-1}.

The FTIR of the solid dispersions of PRXM: PEG 4000 and PRXM: PEG 6000 (1:1) still showed peaks for O-H as very broad peak at 3453 cm^{-1} and for N-H at 3334 cm^{-1}. This indicates that the physical mixture spectra were only the summation of PRXM and PEG spectra and reflected that there was no interaction between PRXM and PEG physical mixtures.

The same phenomenon was detected when we used PRXM: SLS (1:1) as physical mixture which indicated that the spectrum was only the summation of PRXM and SLS spectra and revealed that there was no interaction between them.

FTIR spectra of PVP K30 and PVP K90 showed broad peaks at about 3454 - 3442 cm^{-1}, in addition to sp3 C-H stretching at 2955 - 2954 cm^{-1} and strong acidic carbonyl at 1655 – 1654 cm^{-1}. The FTIR spectra of the solid dispersion PRXM : PVP K30 and PRXM : PVP K90 displayed differences in shape and position of the characteristic peaks of PVP. The broad peak of PVP which was completely covered in the physical mixture spectra and the change in the shape and position of the amidic carbonyl were attributed to a solid state hydrogen bonding interaction between PRXM and PVP.

3.5 In Vitro Release of PRXM Solid Dispersions from Hard Gelatin Capsule

Fig. 3 showed the in vitro release of pure PRXM and the prepared PRXM solid dispersion formulae from 1 PEG4000 to 4 PEG4000(S) using PEG 4000 with or without the addition of 2% SLS. The influence of both PEG 4000 and SLS was studied on the in vitro release of PRXM from hard gelatin capsule.

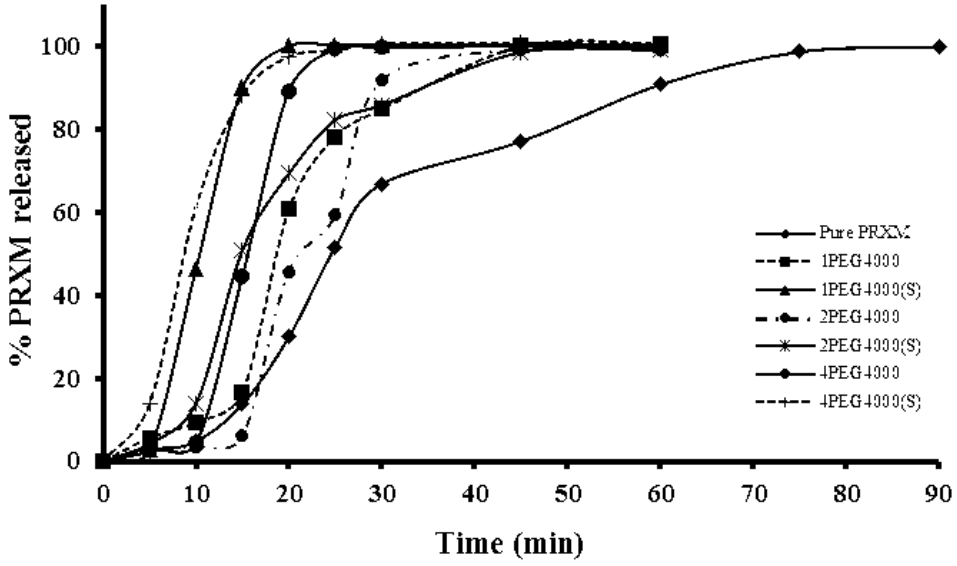

Fig. 3. The in vitro release of PRXM solid dispersions with PEG 4000 at different ratios with or without SLS

Formulae 1 PEG4000, 2 PEG4000, and 4 PEG4000 showed that the time required for 100% release was found to be 60 minutes for 1 PEG4000 and 75 minutes for both 1 PEG4000(S) and 2 PEG4000. To differentiate between 2 PEG4000 and 4 PEG4000, 99.13% and 99.70%

was released after 60 minutes, respectively. The rank order for the in vitro release of PRXM solid dispersion using PEG 4000 was as the following: 1:1 > 1:4 > 1:2.

Formulae 1 PEG4000(S), 2 PEG4000(S), and 4 PEG4000(S) contain similar PRXM-PEG 4000 ratios as above with the addition of 2% SLS. It was found that 100% of PRXM released was obtained after 25 minutes for 1 PEG4000(S) while was found to be 30 minutes for 4 PEG4000(S). After 60 minutes 2 PEG4000(S) was found to release 98.91% of PRXM. This shows that the best formula for the above set was 1 PEG4000(S) followed by 4 PEG4000(S) and then 2 PEG4000(S).

Fig. 4 showed the in vitro release of pure PRXM and the prepared PRXM solid dispersion formulae from 1 PEG6000 to 4 PEG6000(S) using PEG 6000 with or without the addition of 2% SLS.

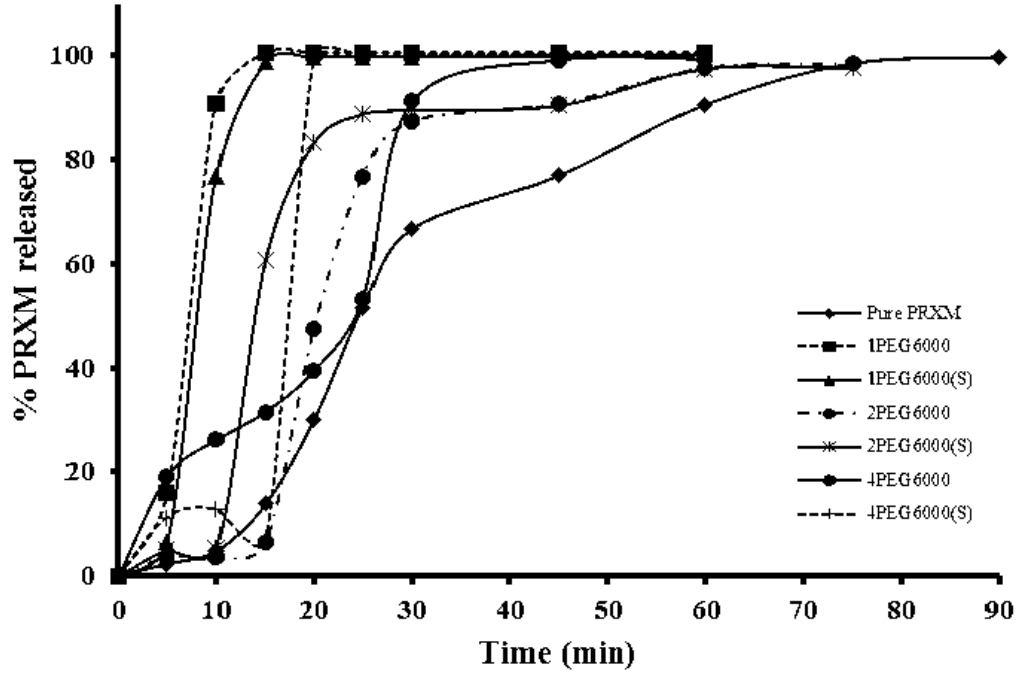

Fig. 4. The in vitro release of PRXM solid dispersions with PEG 6000 at different ratios with or without SLS

One hundred percent of PRXM released in about 15 minutes for 1 PEG6000 and 60 minutes for 4 PEG6000, and 1 PVP-K90 showed after 75 minutes the release of 98.54% of PRXM from the solid dispersion from the hard gelatin capsules. The rank order for the in vitro release of PRXM solid dispersion was as the following: 1:1 > 1:4 > 1:2.

In presence of 2% SLS the release of 100% PRXM was after 45 minutes for 1 PEG6000(S) and after 30 minutes for 4 PEG6000(S). This shows that the best formula for the above set was 4 PEG6000(S) followed by 1 PEG6000(S) and then 2 PEG6000(S). It was found that the addition of SLS with this drug to polymer ratios decreased the release rate of the PRXM from the solid dispersion, while with ratio 1:4, the addition of the SLS increased the rate of release of PRXM.

Fig. 5 showed the in vitro release of pure PRXM and formulae 1 PVP-K30 to 4 PVP-K30(S) of PRXM solid dispersion. These data show the effect of PVP K30 to drug ratio on the release rate of PRXM and the effect of the addition of 2% SLS on the release rate.

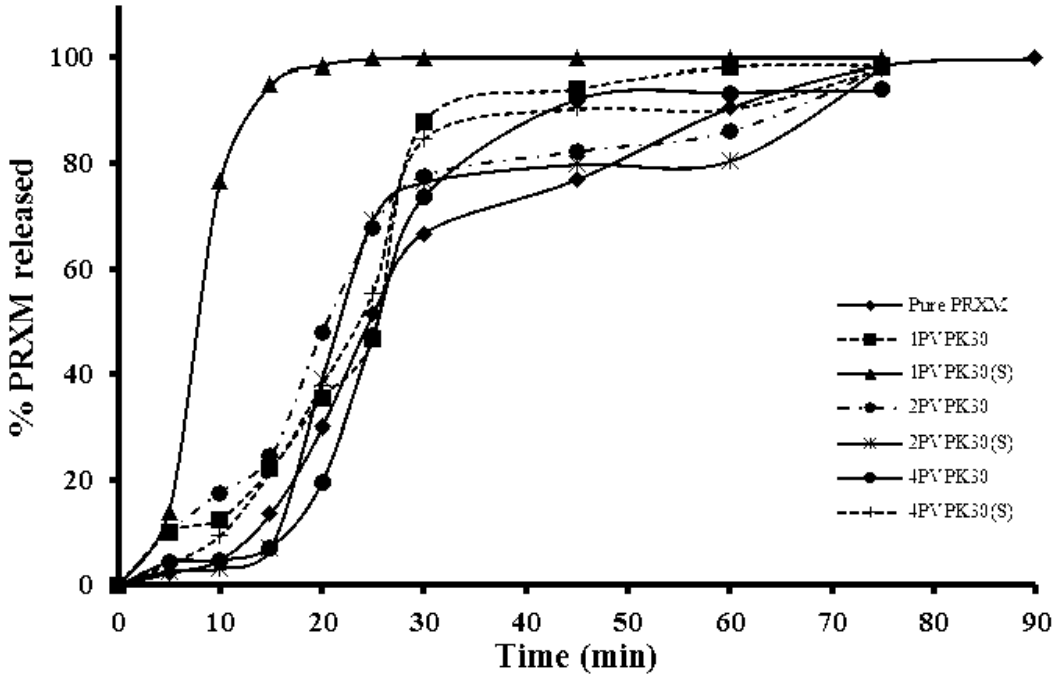

Fig. 5. The in vitro release of PRXM solid dispersions with PVP K30 at different ratios with or without SLS

Formulae 1 PVP-K30, 2 PVP-K30, and 4 PVP-K30 showed almost complete drug release after 60 minutes for 1 PVP-K30, and 2 PVP-K30. After 75 minutes 1 PVP-K30 released 98.50% and 2 PVP-K30 released 98.3 of PRXM. 4 PVP-K30 released only 94% of the drug in 75 minutes , this indicated that the best in vitro release results of PRXM solid dispersions of PVP K30 polymer were from 1:1 > 1:2 > 1:4 drug to polymer ratio, respectively.

In formulae containing 2% SLS the release of 100% PRXM was after 30 minutes for 1 PVP-K30(S). After 75 minutes 2 PVP-K30(S) released 98.50% and 4 PVP-K30(S) released 98.10%. This indicated that the best drug to PVP K30 ratio in presence of 2% SLS was 1:1, followed by 1:2 then 1:4.

It was found also that the addition of the SLS increased the release of PRXM in all drug polymer ratios.

Fig. 6 showed the in vitro release of pure PRXM and formulae 1 PVP-K90, 2 PVP-K90, and 4 PVP-K90. The time required for 100% PRXM release was found to be 60 minutes for 1 PVP-K90, and more than 75 minutes for 2 PVP-K90 and 4 PVP-K90. To differentiate between 2 PVP-K90 and 1 PEG4000(S), after 75 minutes the release of 2 PVP-K90 was found to be 99.32%, and only 78.33% were released from 4 PVP-K90. The rank order for the in vitro release of PRXM solid dispersion: 1:1 > 1:2 > 1:4.

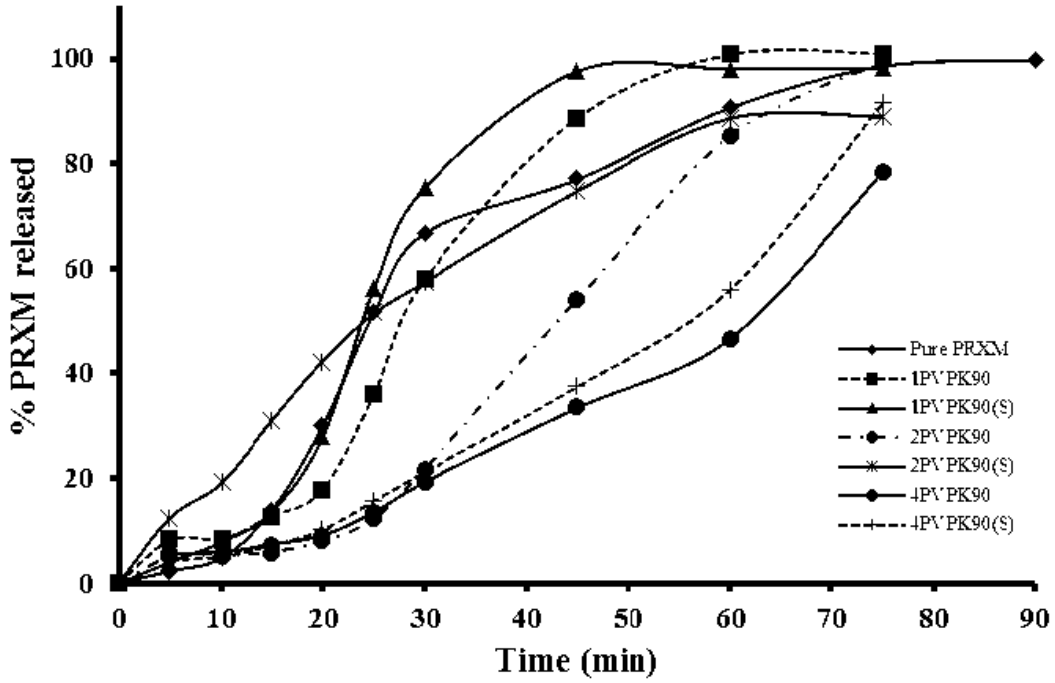

Fig. 6. The in vitro release of PRXM solid dispersions with PVP K90 at different ratios with or without SLS

In presence of 2% SLS, after 75 minutes 1 PVP-K90(S) released 98.18%, 2 PVP-K90(S) released 88.92%, and 4 PVP-K90(S) released 91.44%. Drug to PVP K90 ratio of 1:1 with 2% SLS gave the best results then 1:4 then 1:2.

The addition of 2% SLS decreased the release rate in formulae containing drug polymer ratios of 1:1 and 1:2, while in 1:4 formulae the SLS increased the release rate of PRXM.

The rank order for the in vitro release of PRXM solid dispersions using different drug : polymer ratios from hard gelatin capsules is shown in Table 3. PRXM solid dispersion formulae can be arranged , in descending order, as follows: 1 PEG6000, 4 PEG4000(S), 1 PEG4000(S), 4 PEG6000(S), 1 PEG6000(S), 1 PVP-K30(S), 4 PEG4000, 1 PEG4000, 2 PEG4000, 4 PEG6000, 2 PEG4000(S), 2 PEG6000(S), 2 PEG6000, 1 PVP-K30, 1 PVP-K90, 1 PVP-K90(S), 2 PVP-K30, 4 PVP-K30(S), 4 PVP-K30, 2 PVP-K30(S), 2 PVP-K90(S), 2 PVP-K90, 4 PVP-K90(S), 4 PVP-K90.

This results was consistent with research found that solid dispersions containing PEG 6000 and SLS showed a significant increase in dissolution rate with an increase in PEG 6000 and the solubilizer SLS [45].

The effect of the formation of PRXM as a solid dispersion using spray drying and precipitation with compressed anti solvent, with PVP 25 as a polymer was studied by Wu et al., they found that the dissolution rate is higher than that of the pure drug [46].

Das et al. studied the in vitro release of the PRXM solid dispersion in PEG 6000 and eudraget RL-100 in the ratios 1:1, 1:3 and 1:5 and found that the best dissolution results were for formula in which drug to PEG 6000 ratio was 1:5, which released about 95% in 60 minutes in dissolution medium of pH 1.2 and paddle with speed 50 rpm. The formula with PRXM : PEG 6000 with ratio 1:1 released 69% in 60 minutes and the formula with ratio 1:3 released 82.44% in one hour [47].

Table 3. Rank order for the in vitro release of PRXM solid dispersions from hard gelatin capsules

Formula	% release of PRXM				Ranking order	
	20 (min)	30 (min)	45 (min)	60 (min)	Total	Rank
1 PEG4000	10	14	7	4	35	8
1PEG4000(S)	2	3	4	6	15	3
2 PEG4000	13	8	10	11	42	9
2 PEG4000(S)	9	13	11	12	45	11
4 PEG4000	7	7	8	9	31	7
4 PEG4000(S)	6	2	1	3	12	2
1 PEG6000	1	1	1	2	5	1
1 PEG6000(S)	3	5	5	7	20	5
2 PEG6000	12	12	15	15	54	13
2 PEG6000(S)	8	10	16	16	50	12
4 PEG6000	15	9	9	10	43	10
4 PEG6000(S)	4	4	3	5	16	4
1 PVP-K30	18	11	13	13	55	14
1 PVP-K30(S)	5	6	6	8	25	6
2 PVP-K30	11	16	19	20	66	17
2 PVP-K30(S)	16	17	20	22	75	20
4 PVP-K30	20	19	14	17	70	19
4 PVP-K30(S)	17	15	17	18	67	18
1 PVP-K90	21	20	18	1	60	15
1 PVP-K90(S)	19	18	12	14	63	16
2 PVP-K90	24	22	22	21	89	22
2 PVP-K90(S)	14	21	21	19	75	20
4 PVP-K90	23	23	24	24	94	24
4 PVP-K90(S)	22	24	23	23	92	23

3.6 Kinetic Treatment for the In Vitro Release of PRXM from Hard Gelatin Capsules

The kinetic treatment of the in vitro release of PRXM is critical and has to be investigated to achieve an optimal system with desired release characteristics. Furthermore, in vitro release studies are often performed to predict how the delivery system might work in ideal situations, which might give some indication of its in-vivo performance. The dissolution should also be done in the final dosage form of the solid dispersion, so the kinetic parameters were calculated from the dissolution of PRXM solid dispersions contained in hard gelatin capsules.

Table 4 illustrated the kinetic parameters of the in vitro release of PRXM from hard gelatin capsules. Calculating the kinetic parameters for each order or system, the intercept, the slope, the correlation coefficient, the specific rate constant and the half- life were obtained.

Table 4. Kinetic parameters for the in vitro release of PRXM formulae from hard gelatin capsule

PRXM Formula	Intercept	Slope	Correlation Coefficient (r)	K	t½
1 PEG4000	2.96	0.08	-0.961	-0.18	3.75
1 PEG4000(S)	2.01	0.08	-0.946	-0.18	3.83
2 PEG4000	2.46	0.05	-0.952	-0.11	6.58
2 PEG4000(S)	-3.91	2.09	0.899	-3.91	23.91
4 PEG4000	2.09	0.06	-0.862	-0.13	5.29
4 PEG4000(S)	2.17	0.08	-0.973	-0.18	3.83
1 PEG6000	1.06	0.06	-0.814	-0.15	4.65
1 PEG6000(S)	1.47	0.07	-0.898	-0.16	4.23
2 PEG6000	2.20	0.03	-0.979	-0.07	10.45
2 PEG6000(S)	1.91	0.02	-0.933	-0.05	12.95
4 PEG6000	2.43	0.05	-0.949	-0.11	6.51
4 PEG6000(S)	1.74	0.06	-0.852	-0.15	4.74
1 PVP-K30	2.24	0.03	-0.968	-0.07	9.96
1 PVP-K30(S)	1.45	0.06	-0.908	-0.13	5.24
2 PVP-K30	2.13	0.02	-0.954	-0.05	13.78
2 PVP-K30(S)	2.19	0.02	-0.923	-0.05	13.50
4 PVP-K30	2.17	0.02	-0.950	-0.05	14.08
4 PVP-K30(S)	2.17	0.02	0.985	-0.06	12.57
1 PVP-K90	-2.81	1.60	0.954	-2.81	31.30
1 PVP-K90(S)	-2.79	1.54	0.907	-2.79	32.42
2 PVP-K90	-52.92	16.34	0.934	16.34	9.36
2 PVP-K90(S)	15.41	1.15	0.960	15.41	43.55
4 PVP-K90	-31.69	10.66	0.092	10.66	22.00
4 PVP-K90(S)	-39.91	12.84	0.926	12.84	15.17

The best kinetic order for the in vitro release of PRXM formulae can be calculated from the highest values of the obtained correlation coefficients, which are selected and showed in Table 5. It was found that 17 formulae obey the first order kinetics. These formulae are 1 PEG4000, 1 PEG4000(S), 2 PEG4000, 4 PEG4000, 4 PEG4000(S), 1 PEG6000, 1 PEG6000(S), 2 PEG6000, 2 PEG6000(S), 4 PEG6000, 4 PEG6000(S), 1 PVP-K30, 1 PVP-K30(S), 2 PVP-K30, 2 PVP-K30(S) 4 PVP-K30, and 1 PVP-K90(S). Only 3 formulae obey Higuchi's diffusion model. These three formulae are 2 PEG4000(S), 1 PVP-K90 and 2 PVP-K90. Four formulae obeyed zero order reaction; these formulae are 4 PVP-K30(S), 2 PVP-K90, 4 PVP-K90 and 4 PVP-K90(S). For the 24 prepared PRXM solid dispersion formulae the best correlation coefficients were 1 PEG4000 (-0.96), 1 PEG4000(S) (-0.95), 2 PEG4000 (-0.95), 2 PEG4000(S) (0.90), 4 PEG4000 (-0.86), 4 PEG4000(S) (-0.97), 1 PEG6000 (-0.81), 1 PEG6000(S) (-0.90), 2 PEG6000 (-0.98), 2 PEG6000(S) (-0.93), 4 PEG6000 (-0.95), 4 PEG6000(S) (-0.85), 1 PVP-K30 (-0.97), 1 PVP-K30(S) (-0.91), 2 PVP-K30 (-0.95), 2 PVP-K30(S) (-0.92), 4 PVP-K30 (-0.95), 4 PVP-K30(S) (-0.97), 1 PVP-K90 (0.96), 1 PVP-K90(S) (- 0.95), 2 PVP-K90 (0.98), 2 PVP-K90(S) (0.99), 4 PVP-K90 (0.97), and 4 PVP-K90(S) (0.97).

Table 5. Kinetic parameters for the degradation of PRXM from the prepared solid dispersions in hard gelatin capsule at 40ºC

Formula	Zero – order at 40ºC				
	I	S	r	K	t½
1 PEG4000	-0.31	0.26	0.997	0.26	191.15
1 PEG4000(S)	-0.05	0.19	0.995	0.19	264.35
2 PEG4000	0.15	0.23	0.991	0.23	221.94
2 PEG4000(S)	0.17	0.21	0.994	0.21	240.38
4 PEG4000	-0.32	0.24	0.996	0.24	212.77
4 PEG4000(S)	-0.03	0.18	0.995	0.18	275.81
1 PEG6000	-0.26	0.34	0.989	0.34	147.43
1 PEG6000(S)	-0.21	0.23	0.992	0.23	221.24
2 PEG6000	-0.15	0.24	0.998	0.24	205.16
2 PEG6000(S)	-0.29	0.25	0.995	0.25	202.55
4 PEG6000	-0.30	0.24	0.999	0.24	204.80
4 PEG6000(S)	-0.34	0.25	0.998	0.25	196.41
1 PVP-K30	0.04	0.24	0.999	0.24	206.25
1 PVP-K30(S)	-0.19	0.32	0.994	0.32	154.46
2 PVP-K30	-0.47	0.30	0.999	0.30	169.16
2 PVP-K30(S)	-0.38	0.27	0.997	0.27	186.07
4 PVP-K30	-0.34	0.26	0.992	0.26	189.91
4 PVP-K30(S)	-0.02	0.22	0.999	0.22	227.72
1 PVP-K90	0.10	0.23	0.993	0.23	213.41
1 PVP-K90(S)	-0.13	0.24	0.998	0.24	206.98
2 PVP-K90	-0.12	0.27	0.998	0.27	186.07
2 PVP-K90(S)	0.09	0.17	0.998	0.17	286.41
4 PVP-K90	-0.17	0.28	0.997	0.28	180.60
4 PVP-K90(S)	-0.26	0.26	0.997	0.26	189.19

Several mechanisms have been proposed to account for the increase in the dissolution kinetics of drugs from PEG and PVP solid dispersions. These mechanisms include the carrier controlled dissolution [48-50], the continuous drug layer formation [49] and that involving the release of intact particles with dissolution occurring over a large surface area [51]. The latter mechanism has been suggested to be important at low drug levels. It is also clear that a modification of the surface properties and hence a reduction of the value of the contact angle which improves the wettability of the powder should lead to an increase of dissolution kinetics.

An improvement of wettability of the powder could result from the formation of a film of polyethylene glycol around the drug substance particles which modifies the hydrophobicity of their surfaces [52]. Which mechanism is involved in the increase in the dissolution kinetics of PRXM from PEG 6000, PEG 4000, PVP K30 or PVP K90 dispersions could not be at present established.

3.7 Stability Studies

Since the higher dissolution rates could be due to drug adsorption on material with elevate surface area and on the lack of the drug in a crystalline form storage or one of the other previously mentioned mechanisms, stability studies were conducted in order to verify the physical stability of adsorbed PRXM. First, the effect of temperature was checked. In fact, the temperature increases molecule energy and motion with possible breakage of the light interactions between matrix and drug molecules.

The percent un-degraded PRXM in the 24 prepared solid dispersion formulae are plotted against time as illustrated in Figs. 7-10, each figure shows the percent un-degraded of the drug in six formulae prepared with the same polymer at the two elevated temperatures 40ºC and 60ºC.

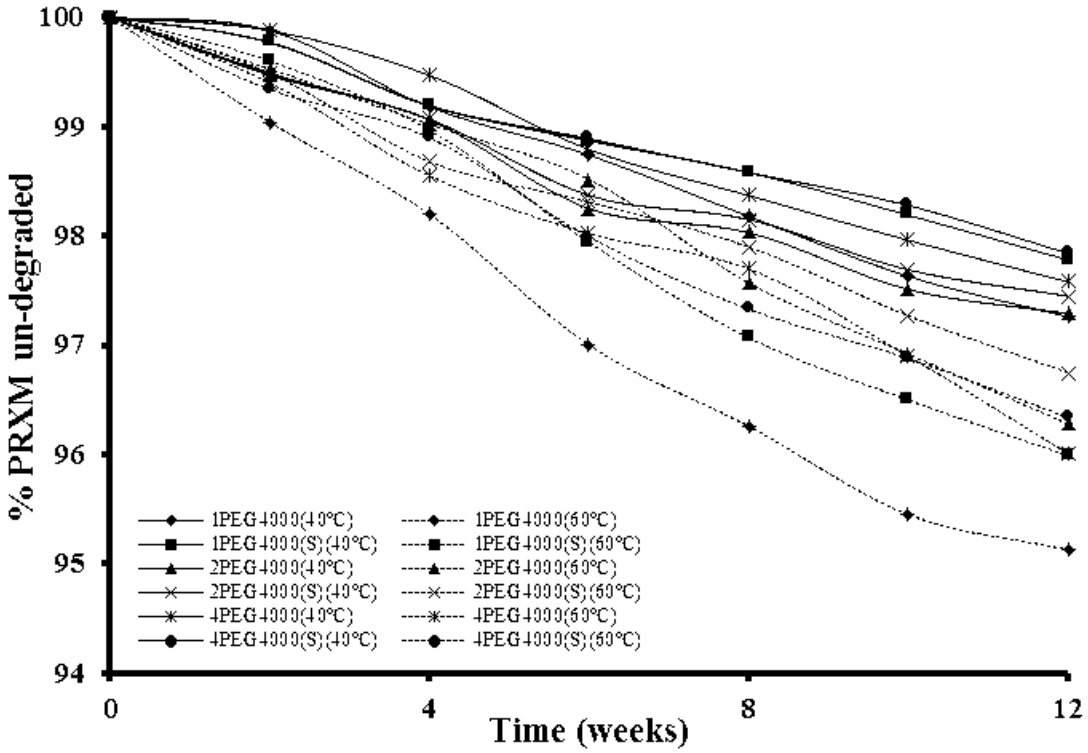

Fig. 7. % PRXM un-degraded at 40ºC & 60ºC (formulae prepared with PEG4000 at different ratios with or without SLS)

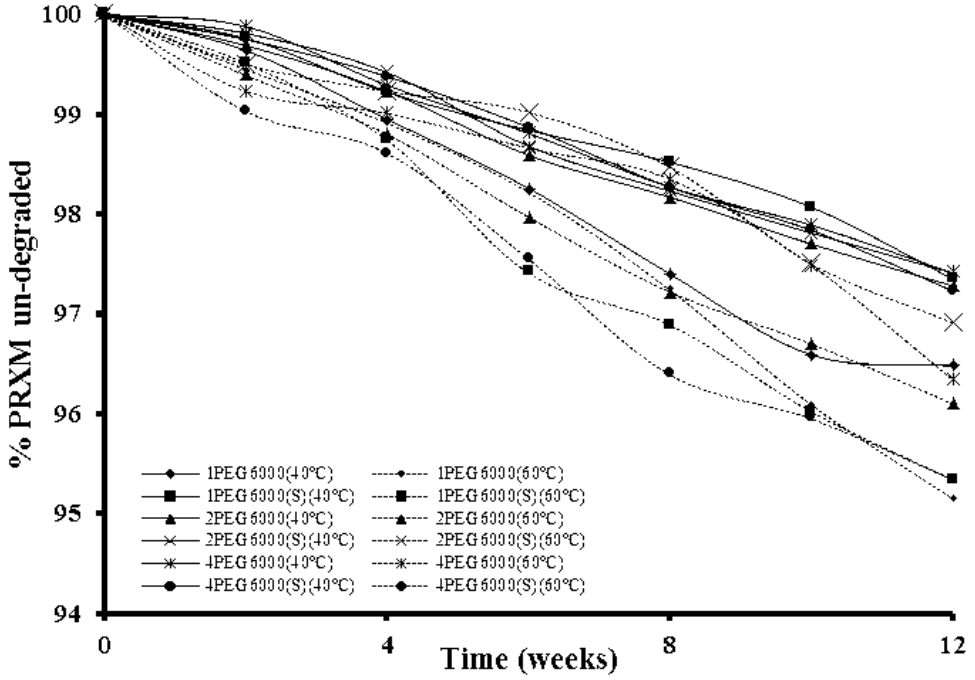

Fig. 8. % PRXM un-degraded at 40ºC & 60ºC (formulae prepared with PEG6000 at different ratios with or without SLS)

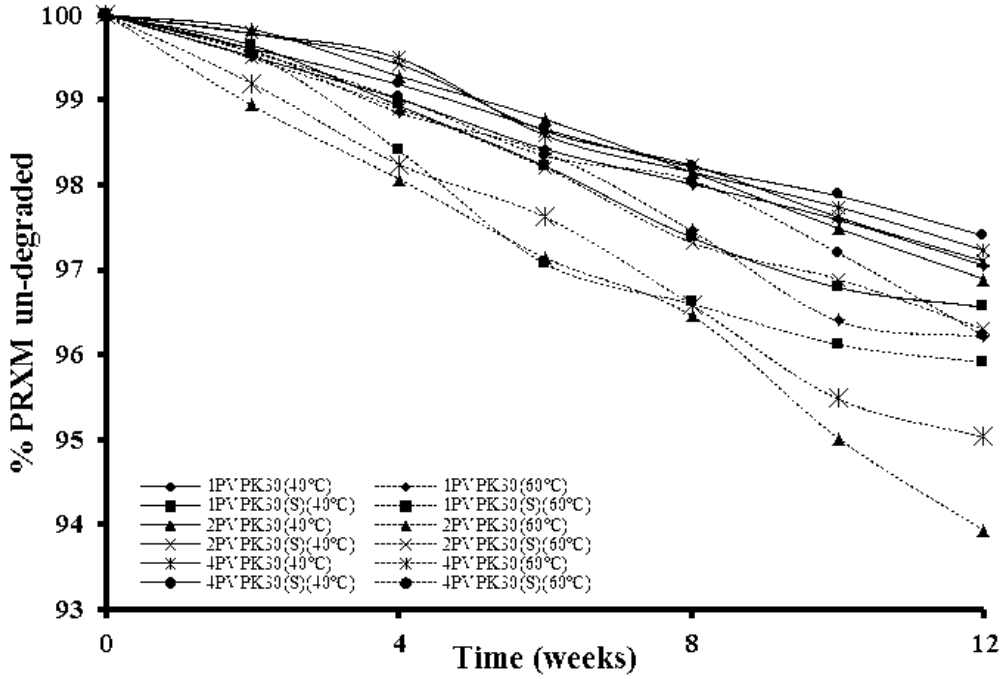

Fig. 9. % PRXM un-degraded at 40ºC & 60ºC (formulae prepared with PVP K30 at different ratios with or without SLS)

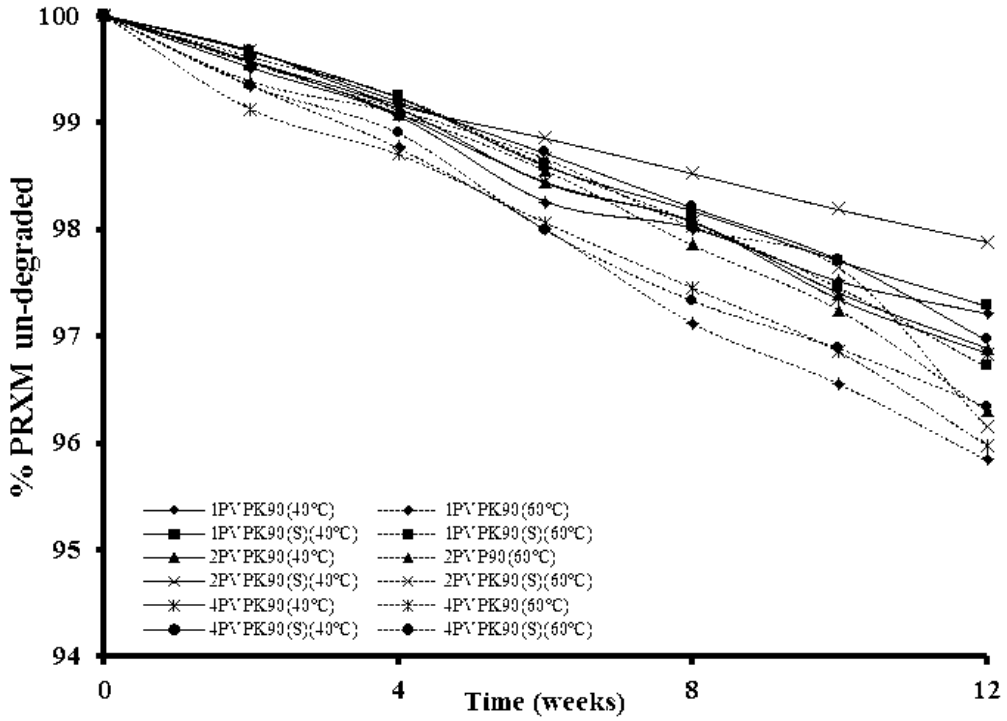

Fig. 10. % PRXM un-degraded at 40ºC & 60ºC (formulae prepared with PVP K90 at different ratios with or without SLS)

The data in Table 5 showed the kinetic parameters for the degradation of PRXM in hard gelatin capsules at 40ºC. The kinetic parameters of the degradation of PRXM from hard gelatin capsules at the second elevated temperature 60ºC, are stated in Table 6. The kinetic treatment was calculated by plotting the time in weeks versus the percent of PRXM degraded for zero order, by plotting the time in weeks versus log percent of PRXM un-degraded for first order and by plotting the time in weeks versus the reciprocal of the percent of PRXM un-degraded for second order.

The degradation of PRXM was very slow at the two elevated temperatures chosen which indicated chemical stability of PRXM in the solid dispersions formulae prepared with the four different polymers.

The obtained results were in a good agreement with the work done by Pan et al. [53].

The amount degraded of PRXM were found to be, after the end of the accelerated stability testing (12 weeks), 2.74%, 2.22%, 2.71%, 2.55%, 2.42%, 2.16%, 3.52%, 2.65%, 2.72%, 2.59%, 2.59%, 2.77%, 2.95%, 3.44%, 3.11%, 2.9%, 2.77%, 2.6%, 2.79%, 2.72%, 3.11%, 2.12%, 3.16%, 3.04% for the 24 formulae of PRXM solid dispersion, respectively at 40^{o}C. The amount of PRXM degraded at 60^{o}C were found to be 4.87%, 4.01%, 3.72%, 3.25%, 3.99%, 3.66%, 4.85%, 4.66%, 3.9%, 3.09%, 3.66%, 4.66%, 3.79%, 4.09%, 6.07%, 3.7%, 4.97%, 3.78%, 4.16%, 3.29%, 3.7%, 3.85%, 4.02%, 3.66%, respectively.

Table 6. Kinetic parameters for the degradation of PRXM from the prepared solid dispersions in hard gelatin capsule at 60ºC

Formula	Zero – order at 60°C				
	I	S	r	K	t½
1 PEG4000	0.30	0.41	0.995	0.41	122.63
1 PEG4000(S)	-0.31	0.38	0.994	0.38	132.93
2 PEG4000	-0.32	0.34	0.996	0.34	148.94
2 PEG4000(S)	0.10	0.26	0.995	0.26	190.84
4 PEG4000	0.01	0.32	0.991	0.32	157.52
4 PEG4000(S)	0.03	0.31	0.998	0.31	161.14
1 PEG6000	-0.60	0.44	0.992	0.44	113.12
1 PEG6000(S)	0.03	0.39	0.992	0.39	128.30
2 PEG6000	-0.14	0.34	0.994	0.34	145.23
2 PEG6000(S)	-0.31	0.27	0.969	0.27	187.27
4 PEG6000	-0.11	0.28	0.950	0.28	181.16
4 PEG6000(S)	0.10	0.39	0.989	0.39	126.86
1 PVP-K30	-0.33	0.36	0.989	0.36	139.05
1 PVP-K30(S)	0.18	0.36	0.988	0.36	137.47
2 PVP-K30	-0.14	0.50	0.992	0.50	99.74
2 PVP-K30(S)	-0.14	0.33	0.997	0.33	153.11
4 PVP-K30	-0.04	0.43	1.000	0.43	116.24
4 PVP-K30(S)	-0.34	0.32	0.989	0.32	154.53
1 PVP-K90	-0.10	0.36	0.998	0.36	139.94
1 PVP-K90(S)	-0.32	0.29	0.996	0.29	171.57
2 PVP-K90	-0.23	0.31	0.988	0.31	161.89
2 PVP-K90(S)	-0.40	0.32	0.968	0.32	158.51
4 PVP-K90	0.12	0.31	0.995	0.31	160.11
4 PVP-K90(S)	0.03	0.31	0.995	0.31	161.14

These results were consistent with Ingkatawornwong et al. who studied the aging of PRXM – PVP solid dispersions. They investigated the stability of PRXM: PVP K17 and K30 solid dispersions after storage for 12 months at 45ºC and ambient temperature.

Very minor decreases in dissolution rates of aged solid dispersions were found which might be due to the coarsening of the particles. Dissolutions of these amorphous solid dispersions after aging for 12 months still showed about 40-fold increase in dissolution in 5 min compared to pure drug [54].

Wu and coworkers showed that in relation to PRXM stability the effect of temperature is approximately in the same order of magnitude as the PRXM: PVP ratio [55].

Pan and colleagues studied the solid dispersion systems of insoluble PRXM in PEG 4000 and in urea which were prepared by fusion and solvent methods. The storage testing showed that all dispersions were stable, except that uptake of water during storage may occur in the PEG system [53].

Accelerated stability studies of solid dispersion of valdecoxib with PVP K 30 and PEG 4000 does not show any significant change in the drug content and dissolution profile in 6 months study period [56].

The best kinetic order for the stability study of PRXM formulae can be calculated from the highest values of the obtained correlation coefficients. It was found that all PRXM formulae obey zero order kinetics.

Half-life and shelf-life were calculated from the following equations and showed in Table 7.

$$t_{1/2} = a / 2k \qquad t_{90} = a / 10K$$

Where (a) is the initial drug amount of drug and K is the stability constant.

The half-lives and T_{90} of drug degradation from the PRXM solid dispersion formulae according to the values calculated for zero order at 20ºC and the rank order of the formulae were shown in Table 7.

Table 7. Data of calculating the shelf lives of PRXM solid dispersions

Formula	K_{40} week^{-1}	K_{60} week^{-1}	Ea cal/mole	k_{20} week^{-1}	$t_{1/2}$ week	t_{90} year	Rank order
1 PEG4000	0.26	0.41	45987.07	0.16	316.56	1.22	11
1 PEG4000(S)	0.19	0.38	7120.10	0.09	577.43	2.22	1
2 PEG4000	0.23	0.34	4132.30	0.14	349.24	1.34	6
2 PEG4000(S)	0.21	0.26	2390.47	0.16	312.48	1.20	12
4 PEG4000	0.24	0.32	3114.03	0.17	299.44	1.15	15
4 PEG4000(S)	0.18	0.31	5566.05	0.10	508.00	1.95	3
1 PEG6000	0.34	0.44	2743.45	0.25	199.22	0.77	23
1 PEG6000(S)	0.23	0.39	5643.31	0.12	410.96	1.58	4
2 PEG6000	0.24	0.34	3578.11	0.16	303.82	1.17	14
2 PEG6000(S)	0.25	0.27	812.40	0.23	221.43	0.85	20
4 PEG6000	0.24	0.28	1270.25	0.21	235.43	0.91	17
4 PEG6000(S)	0.25	0.39	4572.40	0.15	322.80	1.24	10
1 PVP-K30	0.24	0.36	4082.77	0.01	322.82	1.24	9
1 PVP-K30(S)	0.32	0.36	1206.67	0.28	176.33	0.68	24
2 PVP-K30	0.30	0.50	5471.28	0.16	308.36	1.19	13
2 PVP-K30(S)	0.27	0.33	1807.05	0.22	222.27	0.85	19
4 PVP-K30	0.26	0.43	5084.02	0.15	331.77	1.28	8
4 PVP-K30(S)	0.22	0.32	4015.86	0.14	353.82	1.36	5
1 PVP-K90	0.23	0.36	4370.60	0.15	344.76	1.33	7
1 PVP-K90(S)	0.24	0.29	1943.32	0.20	256.18	0.98	16
2 PVP-K90	0.27	0.31	1442.02	0.23	217.97	0.84	21
2 PVP-K90(S)	0.17	0.32	6127.23	0.09	561.05	2.16	2
4 PVP-K90	0.28	0.31	1247.17	0.24	207.09	0.80	22
4 PVP-K90(S)	0.26	0.31	1661.91	0.22	227.04	0.87	18

According to the above results, a rank order of PRXM formulae can be made as follows 1 PEG4000(S) > 2 PVP-K90(S) > 4 PEG4000(S) > 1 PEG6000(S) > 4 PVP-K30(S) > 2 PEG4000 > 1 PVP-K90 > 4 PVP-K30 > 1 PVP-K30 > 4 PEG6000(S) > 1 PEG4000 > 2 PEG4000(S) > 2 PVP-K30 > 2 PEG6000 > 4 PEG4000 > 1 PVP-K90(S) > 4 PEG6000 > 4 PVP-K90(S) > 2 PVP-K30(S) > 2 PEG6000(S) > 2 PVP-K90 > 4 PVP-K90 > 1 PEG6000 > 1 PVP-K30(S).

From the previous results, a conclusive rank order was done as shown in Table 8 where the prepared PRXM solid dispersion formulae were arranged in descending order concerning production yield, drug content, in vitro release of the PRXM solid dispersion from hard gelatin capsules and stability.

Table 8. A total rank order of the prepared PRXM solid dispersion formulae concerning production yield (PY), drug content (DC), micrometrics, in vitro release (IVR) of the hard gelatin capsules and drug stability

Formula	Rank order			Conclusive Rank order	
	RO PY + DC	RO IVR caps.	RO Stability	Total	Rank
1 PEG4000	1	8	11	20	3
1 PEG4000(S)	3	3	1	7	**1**
2 PEG4000	11	9	6	26	5
2 PEG4000(S)	8	11	12	31	8
4 PEG4000	15	7	15	37	12
4 PEG4000(S)	6	2	3	11	2
1 PEG6000	2	1	23	26	5
1 PEG6000(S)	11	5	4	20	3
2 PEG6000	3	13	14	30	7
2 PEG6000(S)	6	12	20	38	14
4 PEG6000	9	10	17	36	11
4 PEG6000(S)	17	4	10	31	8
1 PVP-K30	15	14	9	38	14
1 PVP-K30(S)	13	6	24	43	16
2 PVP-K30	13	17	13	43	16
2 PVP-K30(S)	19	20	19	58	21
4 PVP-K30	18	19	8	45	18
4 PVP-K30(S)	22	18	5	45	18
1 PVP-K90	10	15	7	32	10
1 PVP-K90(S)	5	16	16	37	12
2 PVP-K90	20	22	21	63	23
2 PVP-K90(S)	23	20	2	45	18
4 PVP-K90	24	24	22	70	24
4 PVP-K90(S)	20	23	18	61	22

From this conclusive rank order, it was found that the formula number 1 PEG4000(S) (PRXM-PEG 4000-SLS-1:1) showed excellent results for its production yield and drug content. It was the third highest in vitro release among all prepared formulae. And it was the most stable formula with the highest shelf life among the 24 prepared formulae. It was concluded from these results, that 1 PEG4000(S) is the best formula for preparing PRXM solid dispersion.

4. CONCLUSION

The dissolution characteristics of PRXM in water may be improved by the formation of solid dispersions with PEG 4000, PEG 6000, PVP K30 and PVP K90 using solvent evaporation method. The addition of 2% SLS increased the in vitro release of most of the formulae. Formulae prepared using PEG 4000 was the most stable formula after a 3 months of

accelerated stability study. Degradation of PRXM was found to obey the zero order kinetics in all formulae. It was found that the formula containing PRXM : PEG 4000 in a ratio 1:1 with 2% SLS was the best formula among the 24 prepared formulae.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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