

FORMULATION AND *IN VITRO* EVALUATION OF PIROXICAM MICROSPONGE AS A TABLET

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ABSTRACT

Objective: Piroxicam is a poor water soluble drug; an effort had been made to enhance their dissolution rate through formulating it as a microsp sponge and then fabricated as a tablet for oral administration.

Methods: Piroxicam microsponges were prepared by quasi-emulsion solvent diffusion method using Eudragit RS100, RL100, S100 with different drug-polymer ratios, three different types of inner phase solvent were used, along with various volumes of the selected organic solvent, the prepared formulas were examined for its production yield, loading efficiency, particle size and *in vitro* drug release for formulas have excellent physical properties. Optimum formula that had fast release profile was further fabricated into a tablet using direct compression method, two types of disintegrants along with two different amounts were used, also the addition of microcrystalline cellulose was examined.

Results: The results showed that as the ratio of drug to polymer was increased, the production yield and loading efficiency were enhanced, but the particle size had an inverse relationship. Among the three types of solvent, ethanol was most preferable one; 5 ml of ethanol was most favorable. PF13 (containing Eudragit RS100) have the rapid release profile. No any chemical interaction was observed, microsp sponge with spherical shape, porous structure was obtained. The prepared tablets have acceptable physical parameters. A dramatic enhancement in the dissolution rate as compared with the pure piroxicam tablet was shown, as well as release profile follows Hixson-Crowell kinetic with non Fickian diffusion.

Conclusion: Microsp sponge may represent a promising way to increase the dissolution rate of poorly water-soluble drug.

Keywords: Piroxicam, Microsp sponge, Eudragit RS100, Loading efficiency, Crospovidone.

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INTRODUCTION

The oral route is the most desirable way for drug administration due to its convenience and good patient compliance. A drug from its dosage form is absorbed from the gastrointestinal tract, only when it is dissolved in gastric and intestinal fluids. Following administration, poorly water soluble drugs tend to be eliminated from the gastrointestinal tract before being fully dissolved and absorbed into the blood circulation, which results in a slower onset of action or a trouble in achieving the required therapeutic level. During the last decade, more than 40% of the new chemical entities launched in the U. S. pharmaceutical market faced the problem of adequate aqueous solubility [1]. When the bioavailability of a drug substance is limited by its poor solubility, enhancing the dissolution may improve bioavailability. However, when the bioavailability is limited by the intestinal permeability, faster dissolution is not expected to increase bioavailability. Therefore, of the BCS classes, class II drug molecules are the most promising to show enhancement in the bioavailability as a result of increased solubility, so aqueous solubility of a drug make it in a critical limitation to its oral absorption [2].

Microsp sponge technology was developed by Won in 1987 and the original patents were assigned to advanced polymer system [3]. Micro sponges are porous microsphere having interconnected voids of particle size range 5-300 μ m. They are uniform, spherical polymeric particles. Microsp sponge delivery system (MDS) is a unique technology for controlling delivery of drug. MDS technology has been introduced in topical drug products to facilitate a controlled release of active drug into the skin in order to reduce the systemic exposure and minimize local cutaneous reactions to the active drug moieties [4]. Recently microsp sponge system has been shown to increase the rate of solubilization of poorly water-soluble drugs by entrapping such drugs in the microsp sponge system's pores. Because these pores are very small, so the drug moiety is reduced to microscopic particles and so significantly increase surface area thus greatly enhance the rate of solubilization. Piroxicam (PIR) is an oxycam derivative non-steroidal anti-inflammatory drug (NSAID), by interfering with the synthesis of prostaglandins, PIR produces its

effects. The therapeutic action of NSAID is thought to occur by the inhibition of the cyclooxygenase enzyme. Piroxicam is an antipyretic, analgesic and anti-inflammatory agent used in the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, dysmenorrhea, and acute gout [5]. The aim of this study focusing on the preparation of piroxicam microsponges in order to enhance the solubility and dissolution rate, subsequent evaluation of different variables affecting the Microsp sponge formulation, select the optimum one that will be further incorporated into tablet and then study the effect of different concentration and composition of additives on the release profile of piroxicam from the prepared tablet.

MATERIALS AND METHODS

Materials

Piroxicam was kindly supplied from al-Safa drug industry, Iraq, Eudragit RS 100, Eudragit RL100; Eudragit S100 was purchased from Rhom Pharma Germany. Dichloromethane was obtained from GCC Analytical Reagent, UK. Ethanol was purchased from Sigma-Aldrich, Germany. Methanol was obtained from Thomas Baker chemical, Mumbai, India. Glycerol was obtained from BDH, England. Crospovidone was purchased from 3B pharmaceutical (Wuhan) International Co. Ltd, China. Sodium starch glycolate was gifted from Samarra Drug Industries (SDI), Iraq. Microcrystalline cellulose (Avicel PH 102) was gifted from al-Hekma Drug Industry, Jordan. Magnesium stearate was obtained from Riedel-De-Haen AG Seelze, Germany. Lactose and Hydrochloric acid were obtained from Labort, Mumbai, India. Polyvinyl alcohol, disodium hydrogen phosphate and potassium dihydrogen phosphate were obtained from SD fine-Chem limited, Mumbai, India.

Methods

Preparation of piroxicam microsp sponge

Piroxicam micro sponges were prepared by quasi emulsion solvent diffusion method. In this method the internal phase consists of Eudragit (RS100, RL100, S100) dissolved in an organic solvent

(ethanol, dichloromethane (DCM) and methanol) then glycerol was added as plasticizer and followed by the addition of piroxicam under ultra sonication at 35°C for 15 min. The internal phase was then poured into the external phase (0.05% polyvinyl alcohol in distal water) after one hour of stirring by mechanical stirrer (from Copley scientific, UK) at a rate of 500 rotations per minute (r. p. m); the micro sponges were formed due to the removal of organic solvent from the system. The micro sponges were filtered and dried at 40 °C for overnight. The composition of each micro sponge formulation is shown in table 1. The fabricated micro sponge were evaluated for production yield, loading efficiency, particle size and *in vitro* dissolution studies were done for the formulas having the best

physical properties. Formula of highest release profile was further subjected to kinetic release model, FTIR, differential scanning calorimetry, X-ray diffractometry and scanning electron microscopy.

Determination of production yield

The production yield of the Microsponge was determined by calculating accurately the initial weight of the raw materials and the last weight of the Microsponge obtained after drying [6].

$$\text{Production yield (PY)} = \frac{\text{Final obtained mass of microsponges}}{\text{initial mass of polymer and drug}} \times 100$$

Table 1: Composition of piroxicam microsponges

Code	PIR (g)	Eudragit RS100 (g)	Eudragit RL100 (g)	Eudragit S100 (g)	DCM (ml)	Ethanol (ml)	Methanol (ml)	*PVA solution (0.05% w/v)	*Glycerol (ml)	*Stirring rate (r. p. m)	* Rotation time (h)
PF1	0.3	0.1	----	----	----	2.5	----	100	0.5	500	1
PF2	0.6	0.1	----	----	----	2.5	----	100	0.5	500	1
PF3	0.9	0.1	----	----	----	2.5	----	100	0.5	500	1
PF4	0.3	----	0.1	----	----	2.5	----	100	0.5	500	1
PF5	0.6	----	0.1	----	----	2.5	----	100	0.5	500	1
PF6	0.9	----	0.1	----	----	2.5	----	100	0.5	500	1
PF7	0.3	----	----	0.1	----	2.5	----	100	0.5	500	1
PF8	0.6	----	----	0.1	----	2.5	----	100	0.5	500	1
PF9	0.9	----	----	0.1	----	2.5	----	100	0.5	500	1
PF 10	1.2	0.1	----	----	----	2.5	----	100	0.5	500	1
PF 11	0.9	0.1	----	----	2.5	----	----	100	0.5	500	1
PF 12	0.9	0.1	----	----	----	----	2.5	100	0.5	500	1
PF 13	0.9	0.1	----	----	----	5	----	100	0.5	500	1
PF 14	0.9	0.1	----	----	----	7.5	----	100	0.5	500	1

* Values were kept constant

Determination of loading efficiency

The drug content in the micro sponges was determined using a UV spectrophotometer from EMC LAB, GmbH, Germany. A sample of PIR microsponge (10 mg) was dissolved in 1000 ml of 0.1 N HCL (pH 1.2). The solutions were subsequently diluted (if needed) suitably with the same solution and spectrophotometric absorbance was taken at the corresponding λ max of PIR. The drug content was calculated from the calibration curve and expressed as the loading efficiency [7].

$$\text{Loading efficiency} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100$$

Particle size measurement

The average particle size of PIR loaded micro sponges was determined by using an optical microscope from Olympus, Japan. Minute quantities of microsponges were spread on a clean glass slide and the average particle size was calculated by measuring 100 particles of each batch [8].

$$D_{av} = \sum nd / \sum n$$

Where: D_{av} is the average diameter of particles (μm), n is the number of particles per group, and d is the middle value (μm).

In vitro dissolution study

The *in-vitro* drug release study was carried out using dissolution testing apparatus paddle type (Copley dissolution 8000, Copley scientific, UK). Sample equivalent to (10 mg) of piroxicam is used. The dissolution test was performed using 900 ml of 0.1N HCL (pH 1.2). The formulas were rotated at 50 r. p. m at 37 ± 0.5 °C. The samples were collected at specified time intervals (5, 10, 15, 20, 25, 30, 45, 60, 90 and 120 min) and immediately replaced with fresh dissolution medium to maintain the sink conditions, the sample was filtered through a 0.45 Millipore filter, then the filtrate was diluted

(if necessary) with the same dissolution media. The absorbance of the filtrate was measured by a UV spectrophotometer at the corresponding λ max of piroxicam [9].

Fourier transform infrared (FTIR)

FTIR is an extremely powerful technique in detecting and evaluating any possible chemical interaction between piroxicam and any excipient during microsponge preparation. Moreover, molecular level characterization of microsponge can also be obtained by performing FTIR studies FTIR spectra of the pure PIR and the selected microsponge formula were recorded on potassium bromide disc using an FTIR spectrometer (FTIR-8300 Shimadzu, Japan) to ascertain compatibility [10].

Differential scanning calorimetry (DSC)

DSC can be used to evaluate the physical properties of drugs and also to determine the compatibility of the drug and excipients. Thermal analysis using DSC (thermo-analyzer from LENSEIS) was carried out on pure PIR and the prepared PIR microsponge. Accurately weighed samples (10 mg) were loaded into aluminum pans and sealed. Samples were run at a heating rate of 5 °C/min. over a temperature range 0-300 °C in an atmosphere of nitrogen [11].

X-ray powder diffractometry (PXRD)

To verify the physical state of drug in pure state and the changes in the crystallinity of the PIR microsponge formulation, the PXRD study was carried out by using X-ray diffractometer from Shimadzu Company, Japan. The voltage of 40 Kv and a current of 40 mA of the generator were applied with Cu as the tube anode material. The samples of pure drug and the optimum microsponge formula were analyzed between 5 ° to 60 ° [12].

Scanning electron microscope (SEM)

For morphology and surface topography, the selected microsponge can be coated with gold-palladium under an argon atmosphere at

room temperature and then the surface morphology of the microsponges can be studied by scanning electron microscopy from (Angstrom Advanced Inc., USA) [13].

Formulation of PIR Microsponge tablets

The selected PIR microsponge are further fabricated into a tablet dosage form in order to be administered orally, Different formulas as shown in table (2) were formulated to show the effect of different type and concentration of additive material on the properties of PIR microsponge tablet (as well as pure PIR tablet prepared from the same additive of the selected formula) using a direct compression method as way of tablet preparation. In this method accurately weighed quantities of active ingredient (PIR microsponge corresponding to 10 mg of piroxicam) and the calculated excipients (except Mg stearate) were mixed for 10 min using mortar and pestle after which the remaining material was added and blended for another 2 min. The final mixtures are compressed using a single punch tablet machine.

Pre-compression parameters of PIR microsponge tablet powder

Measurement of angle of repose

Using the fixed funnel method, the angle of repose of the prepared PIR microsponge tablet powder was determined. The following procedure was used to measure the angle of repose, a funnel with the end of the stem cut perpendicular to the axis of symmetry is secured with its tip at a given height (h) (which is maintained at approximately 2-4 cm from the tip of the powder pile in order to minimize the impact of the falling powder on the tip of the cone), above graph paper placed on a flat horizontal surface. The powders were carefully poured through the funnel until the apex of the

conical pile so formed just reached the tip of the funnel; the graph paper was not allowed to vibrate. The tan of the angle was calculated after measuring the radius and the height of the cone of the powders using the following equation [14].

$$\tan \theta = \frac{h}{r}$$

Where θ is the angle of repose, the results were given as a mean \pm SD. of triplicate.

Evaluation of the prepared PIR microsponge tablets

Tablet hardness test

The hardness (force required to break a tablet by diametrical compression) of all the prepared PIR microsponge tablets was measured using a Monsanto hardness tester. Since the minimum practical hardness that provides adequate mechanical resistance is not less than 3 kg, so the hardness of the entire prepared tablet should be kept as possible above this limitation. Results are expressed as a mean \pm SD of triplicate.

Tablet friability

The friability test was done for the PIR microsponge tablets using friabilator apparatus for 4 min at 25 r. p. m. The procedure can be summarized by taking ten pre-cleaned tablets, weighing them all together then placing them inside the tester. After their revolution, they were deducted and weighed again. The friability was calculated as the percent weight loss. If the reduction in the total mass of the tablets is more than 1%, the tablets fail in the friability test the friability percent of the tablet was calculated using the following equation [16].

Table 2: Composition of piroxicam microsponge tablet

Code	Piroxicam microsponge (mg)	Pure piroxicam (mg)	Crospovidone (mg)	Sodium starch glycolate (mg)	Microcrystalline cellulose (Avicel PH 102) (mg)	Magnesium stearate (mg)	Lactose (mg)
PF15	10.2	----	3.4	----	----	1	155.4
PF16	10.2	----	6.8	----	----	1	152
PF17	10.2	----	----	3.4	----	1	155.4
PF18	10.2	----	----	6.8	----	1	152
PF19	10.2	----	6.8	----	4.25	1	147.75
PF20	10.2	----	6.8	----	8.5	1	143.5
PF21	----	10	6.8	----	8.5	1	143.7

$$\% \text{ Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Disintegration time test (DT)

The disintegration test was carried out for the prepared PIR microsponge tablets by using the USP disintegration apparatus from Erwaka, ZT 3-4, Germany, the basket rack assembly containing six open-ended tubes and 10-mesh screen on the bottom was used, these six tubes are filled with 0.1NHCL (pH 1.2). The time in minute required for the complete passing of all fragments of the tablet is recorded as a disintegration time of the tablet [17].

Content uniformity

Five tablets were weighed individually and powdered. The powder equivalent to 10 mg of PIR was weighed and dissolved in 10 ml of 0.1 NHCL (pH1.2) and volume was adjusted to 1000 ml with the same solution. Then the solution was filtered and from this solution 1 ml was taken and diluted with 0.1N HCL (pH1.2) in 100 ml standard volumetric flask. The amount of drug present in each tablet was determined spectrophotometrically at the λ_{\max} of PIR using a UV-spectrophotometer. The percentage content was determined using standard calibration curve equation.

In vitro drug dissolution study

In vitro dissolution studies of the promising PIR microsponge tablets and the ordinary prepared PIR tablet formulations were performed

according to USP XXIII Type-II dissolution apparatus employing a paddle stirrer at 50 r. p. m using 900 ml of 0.1N HCL (pH 1.2) at 37 ± 0.5 °C as dissolution medium. One tablet was used in each test; the aliquot volume of the dissolution medium (5 ml) was withdrawn at specific time intervals (5, 10, 15, 20, 25, 30, 45, 60, 90 and 120 min) and replaced immediately with an equal volume of fresh medium. The samples were filtered through 0.45 μ m millipore filter and analyzed for drug content by measuring the absorbance at piroxicam λ_{\max} using an ultraviolet-visible spectrophotometer. Drug concentration was calculated from the standard calibration curve and expressed as a percent of a cumulative drug release [18].

Kinetic model of drug release

The release profile of piroxicam from both optimum microsponge and the selected PIR microsponge tablet were examined to show the best kinetic release model which has the highest R^2 value that interpret such profile; these models include zero order, first order, Higuchi model, Hixson-Crowell model and Korsmeyer-Peppas model.

Accelerated stability studies

The optimum formula was subjected to the accelerated stability test. The test was performed for 16 w duration and three various temperatures 40 °C, 50 °C, and 60 °C. After that, the samples were taken at 14 d interval and examined for their PIR content spectrophotometrically at corresponding piroxicam λ_{\max} .

Statistical analysis

The results of the experiments are given as a mean of triplicate samples \pm standard deviation and were analyzed according to the one-way analysis of variance (ANOVA) to determine if the differences are statistically significant at ($P < 0.05$) using Microsoft office excel 2010.

RESULTS AND DISCUSSION

Formulation of piroxicam microsponge

Piroxicam loaded microsponges were prepared by quasi-emulsion solvent diffusion method from different types of polymer (Eudragit RS100, RL100 and S100) which are biologically inert, non-irritating, non-mutagenic, non-allergenic, non-toxic and non-biodegradable polymers. As a result, the human body cannot convert them into other substances or break them down, so when these polymers administered orally, they are excreted unchanged with the remaining food [19]. Because of its simplicity and reproducibility, quasi-emulsion solvent diffusion method was used for the preparation of microsponges. Moreover, it has the advantage of avoiding solvent toxicity [20]. The Production yield of all formulas lies between (51.67-96.33), all formulas have an acceptable loading efficiency ranged from (85.18-98), there is a significance difference ($p < 0.05$) between three types of polymer in the case of production yield and loading efficiency. Regarding the particle size of the prepared microsponge the mean lie between (70.34 μm -40.33 μm), the results are depicted in the table (3).

Effect of formulation variables on the production yield and the loading efficiency

A real fact illustrates that the production yields and loading efficiency, enhanced by increasing the drug: polymer ratio. Since in the higher drug: polymer ratios, the available polymer can encapsulate more amount of drug. The highest loading efficiency, the greater amount of drug was encapsulated [21]. An increment in the drug to polymer ratio resulted in the formation of drug crystals over particle surfaces. It is easily deducible from the earlier hypothesis that at a higher drug: polymer ratios, more drugs will reach the surface of the nascent micro sponges being dissolved in the solvents during diffusion. Moreover, as the diffusion of solvents becomes slower with the increase in drug: polymer ratio, so there was more time for the formation of drug crystals [22, 23]. The result showed a significant ($p < 0.05$) increase in the production yield and loading efficiency. Its secretariat to mention that the further increment in the drug polymer ratio will lead to unfavorable results. These findings characterized by decreasing in the production yield and the loading efficiency, this is may be due to the improper amount of polymer available for coating the high concentration of drug [24].

It remains to recall that the difference in the viscosity of the three types of polymer used may lead produce a dissimilar result of microsponge properties.

Concerning solvent type it was found that ethanol significantly ($p < 0.05$) increased the loading efficiency when compared to

dichloromethane and methanol. This may be due to the higher boiling point of ethanol (78.4 °C) compared to dichloromethane (40 °C) and methanol (64.7 °C), so ethanol would evaporate more slowly than dichloromethane. The lower organic solvent evaporation rate led to a lower solvent front kinetic energy, which accordingly decreased the rate of diffusion of the solvent from the inner to the outer phase, so increasing the chance for loading the drug into the polymer [25].

It was clearly visible that upon an increment of ethanol volume, the loading efficiency will be increased; this result may be related to the higher solubilization of drug in ethanol. The high volume of the inner phase solvent resulted in the uniform mixing of drug and solvent which consequently lead to higher loading efficiency [26]. It was hypothesized that with the increase in a solvent ratio, the precipitation of polymer solution droplets gradually became slower, allowing more time for solvent diffusion and subsequent deposition of drug crystals on the particle surface [22]. Moreover, the higher volume of ethanol yields more spongy and porous microsponge. The increased amount of ethanol also causes the precipitation of the drug at the periphery of the microsponge. This may enhance the drug release [27]. The result suggests that the amount of ethanol need to be controlled within an appropriate range to affect not only the formation of quasi-emulsion droplets at the initial stage but also the solidification of drug and polymer in the droplets. The good micro sponges were produced when 5 ml of ethanol was used.

Effect of formulation variable on particle size

It was observed that as the ratio of drug to polymer was increased, the particle size decreased. This result may be attributed to two aspects. First, this could probably be due to the fact that in high drug to polymer ratio, the amount of polymer available per microsponge was comparatively less. Probably in high drug-polymer ratios, less polymer amounts surround the drug and reducing the thickness of polymer wall and micro sponges with smaller size were obtained [28]. Secondly, the least viscous polymer solution that results from minimum polymer fraction. This decrement in viscosity facilitates the breaking of an emulsion into smaller droplets resulting in micro sponges with teeny particle size [29]. It is worthwhile to mention that the production of smaller microsponge may lead to enhance the probability of entrapping the drug molecule since a larger surface area are available and more active place are ready to absorb drug resulting in a preferable loading efficiency[30].

However the particle size was slightly increased (non-significant $p > 0.05$) when ethanol is used, since the other two organic solvents have the high solvent evaporation rate led to a higher solvent front kinetic energy, which accordingly raise the rate of diffusion of the solvent from the inner to the outer phase (the critical parameter determining the particle size), so this will lead to a smaller particle [31].

Regarding the volume of ethanol used, it was concluded that as the volume increased, a smaller microsponge globules are formed. These results may be related to the reduction in the viscosity of the internal phase.

Table 3: Properties of the prepared microsponge

Code	Production yield* (%)	Loading Efficiency* (%)	Particle size means* (μm)
PF1	61.67 \pm 1.44	66.98 \pm 3.39	66.33 \pm 1.52
PF2	69.52 \pm .82	64.37 \pm 1.95	59.33 \pm 2.51
PF3	82.00 \pm 3	88.33 \pm 1.45	53.33 \pm 1.52
PF 4	51.67 \pm 3.81	70.62 \pm 1.26	69.33 \pm 1
PF 5	54.76 \pm 2.18	78.80 \pm 1.5	64.00 \pm .57
PF 6	78.67 \pm 1.15	82.52 \pm 1.61	57.67 \pm 2.08
PF 7	53.33 \pm 1.44	58.18 \pm 2.7	70.34 \pm 1.15
PF 8	61.43 \pm 1.42	73.28 \pm 1.11	66.67 \pm 1.69
PF 9	69.00 \pm 1	76.91 \pm .72	58.57 \pm 2.64
PF10	79.72 \pm 1.73	79.99 \pm 2.75	51 \pm 2.02
PF11	75.67 \pm .57	80.84 \pm 1.96	51.17 \pm 1.52
PF12	78.33 \pm 2.08	83.72 \pm 1.23	53.33 \pm 1.15
PF13	96.33 \pm 2.51	98 \pm .77	40.33 \pm 1.15
PF14	82.00 \pm 2.64	94.81 \pm .42	45.20 \pm 1.05

*All values are expressed as mean \pm SD

In vitro drug dissolution study

The dissolution testing was done for the formulas that have a preferable production yield, loading efficiency and the smaller particle size and also for pure PIR powder, so PF13 and PF14 are examined. The drug release profile of the microsp sponge formulation showed that cumulative percent drug release was high in the 1st half hour (fig. 1). Burst release was observed, which could be due to the surface adsorbed drug and the well-known porous nature of micro sponges, the pores providing channels for drug release [32]. Formula (PF13) Acquire superior dissolution rate in comparison with other formulas and with pure drug, this may be attributed to the fact that the reduction of drug particle size caused an increase in the surface area and consequently enhanced the contact between particles and dissolution medium. The obtained results are in good accordance with Noyes-Whitney equation which states that the diminished particle size lead to an increased dissolution rate [33], also it must be remembered that a little amount of Eudragit RS100 form a smaller micro sponges, and hence shorten the path length in which the drug molecule has to traverse. Another explanation suggested that the low amount of Eudragit RS100 lead to enhance the amount of drug close to surface with a simultaneous reduction in

the amount of drug getting entrapped in the polymer matrix occurs. This leads to raise in the rate of drug release from the microsponges. These findings are in accordance with that obtained by Harsh *et al.* [34]. In the recent year united state food and drug administration provide a guideline in a comparison between the dissolution profiles of pharmaceutical product using similarity and dissimilarity factor (f_2, f_1), in which f_1 values lower than 15 (0–15) and f_2 values greater than 50 (50–100) mean similarity of the dissolution profiles [35]. In the case of PIR microsp sponge formula (PF13) reported as a test and the pure drug as a reference, it was shown that PF13 and pure drug profiles are not similar as f_1 value was higher than 15, whereas their f_2 value was more than 100. Moreover, the amount of drug released at 2 min and the time required to reach 80% of drug released were also studied as shown in the table (4). PF13 was determined as the optimum formula because it had the higher dissolution rate, acceptable production yield, high loading efficiency, and small particle size, so it was subjected to further investigation. The release of PIR from microsp sponge PF13 mainly flows Hixon-Crowell release kinetic as their (R^2) gave a higher value. It was found that the mechanism of drug release is non Fickian diffusion as the release exponent "n" value is more than 0.5 and less than 1 which is the standard value for declaring non Fickian release behavior (fig. 2).

Table 4: Parameter of drug release profile of PIR microsp sponge (PF13)

Code	% Released at 2 (min)	Time to reach 80% of drug released (min)	Dissimilarity factor	Similarity factor
PF 13	14	40	19	167

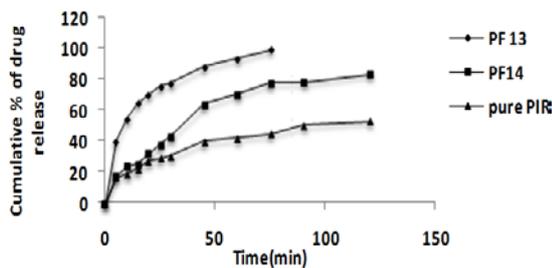


Fig. 1: Dissolution profile of the prepared microsp sponge formulas and pure PIR powder

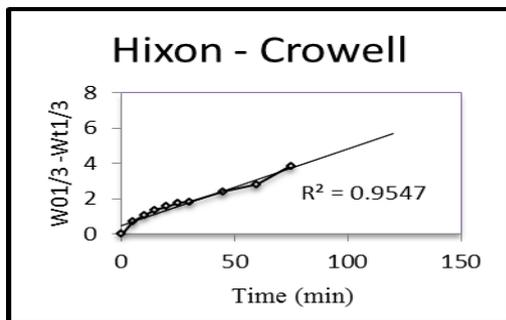


Fig. 2: Release kinetic of the prepared PIR microsp sponge (PF13)

Fourier transforms infrared analysis

The FTIR spectra of PIR were shown in fig. (3 a), the main characteristic peak of PIR was the secondary amine N-H stretching which appeared at 3338 cm^{-1} . It has been reported that piroxicam has two inter convertible crystalline forms, namely the needle and cubic forms. The IR absorption peaks at 1634 cm^{-1} and 1629 cm^{-1} are assigned to the stretching of the amide carbonyl groups of the needle form and the cubic form respectively, the peak at 1529 cm^{-1} is due to the stretching of the second amide band for both crystalline forms of piroxicam. In the present study, the peak at 1629.55 cm^{-1} was found in the IR spectrum of piroxicam, suggesting that the cubic form of piroxicam was used.

The PIR spectra also exhibited other characteristic peaks like, C=N stretching vibration of pyridyl nitrogen assigned at 1577.49 cm^{-1} , C=C stretching of pyridine ring at 1531.2 cm^{-1} , C=C stretching of aromatic ring at 1434.78 cm^{-1} , C-N stretching at 1349.79 cm^{-1} , C-O stretching at 1214.93 cm^{-1} , S(=O)2 stretching at 1149.37 cm^{-1} , SO₂-N stretching at 1064 cm^{-1} , aromatic CH bending at 875.52 cm^{-1} , ortho-disubstituted phenyl at 773.89 cm^{-1} and C-S stretching at 690.39 cm^{-1} [36, 37]. Eudragit RS100 pattern (fig. 3b) showed an ester C=O stretching peak around 1724 cm^{-1} . The pattern of the selected microsp sponge formula (fig. 3c) showed band at 3336.88 cm^{-1} which was related to the N-H stretching and all the original peaks of the pure drug remained without changing, the existence of 1629 cm^{-1} indicates that the piroxicam was fixed in the cubic polymorphic form and no interaction with accidents occurred. Specific changes in IR spectra are not very clear. This could be due to variations in the resonance structure, rotation of a part of a molecule or certain bond, so it was concluded that there is no interaction between piroxicam: Eudragit RS100 after evaporation of the solvent. Similar results were obtained by Adibkia *et al.* [38].

Differential scanning calorimetry (DSC)

According to the DSC thermograms (fig. 4a), pure PIR manifest a sharp characteristic endothermic peak at 201 °C corresponding to the melting point of the drug in the crystalline form, which are the same as reported by other study [39]. Through the study of the DSC curve of PIR microsp sponge (PIR: Eudragit RS100), the thermogram of the selected microsp sponge formula (fig. 4b) showed that the drug remained in its crystalline form and also there was no interaction between the drug and the remaining materials. The drug peak passes away mainly may be due to the lower amount of polymer used in the preparation of PIR microsp sponge (FP13) in comparison to the amount of drug (the drug to polymer ratio used in FP13 is 9:1). Such results revealed that there is no interaction between PIR and another constituent, indicating that the fabrication process used for the preparation did not change the nature of the drug in microsponges. It has remained to recall that the shifting of the endothermic peak to the left may be related to the decrement in the crystallinity of the PIR microsp sponge.

X-ray powder diffractometry

The selected PIR microsp sponge and the pure PIR alone were tested using X-ray powder diffraction device. The characteristic peaks of piroxicam appeared in the 2 θ range (0–60°). The pure drug (fig. 5a) exhibits its characteristic diffraction peaks at various diffraction

angles indicating the presence of crystallinity. On the other hand, the examination of the selected PIR microsp sponge formula shown that there is a clear change in the physical properties of the compound in terms of degree of crystallization indicating the crystalline nature of the drug and this result agreed with that obtained from DSC study. Upon inspection the chart of the selected microsp sponge formula (fig. 5b), there was an interesting reduction in the intensity of the peaks

with the survival of most of them with no appearance of new diffraction peaks which rules out any chemical interaction between the components, suggesting that the overall structure of the compound was not changed and it was identical to what were obtained from the DSC and FTIR. These findings suggested that Piroxicam crystal habit was modified to show improved micrometric properties.

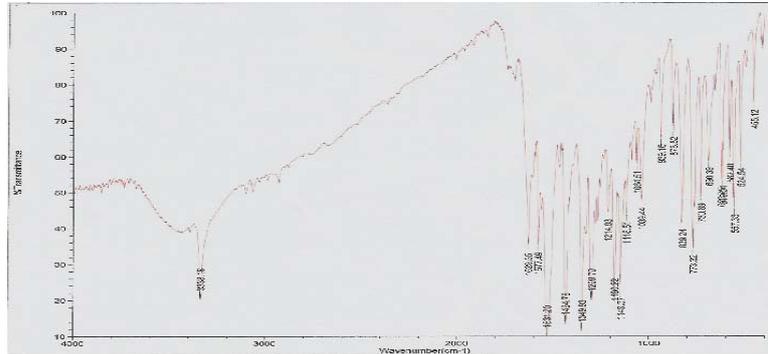


Fig. 3a: FTIR spectra of pure PIR powder

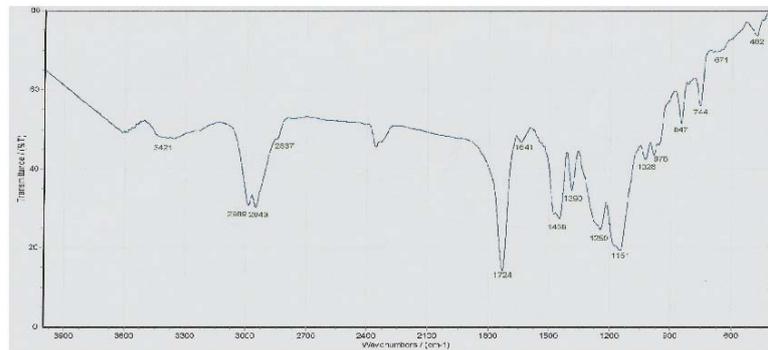


Fig. 3b: FTIR of eudragit RS100

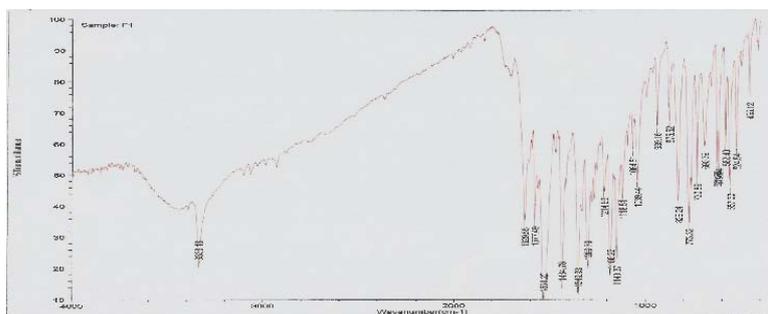


Fig. 3c: FTIR of the prepared PIR microsp sponge (PF 13)

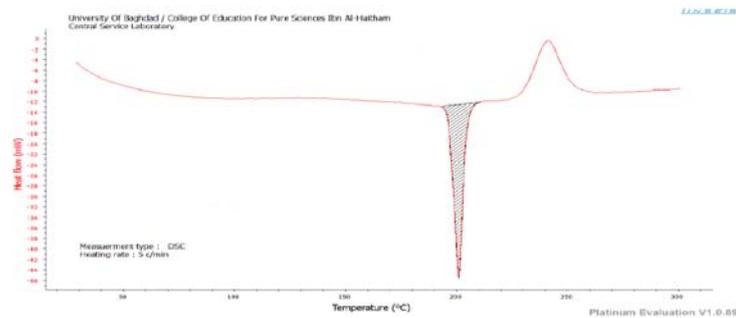


Fig. 4a: DSC thermogram of pure PIR powder

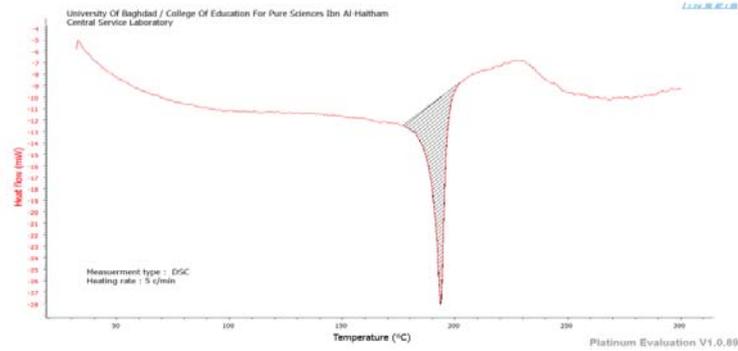


Fig. 4b: DSC thermogram of the prepared microsp sponge (PF13)

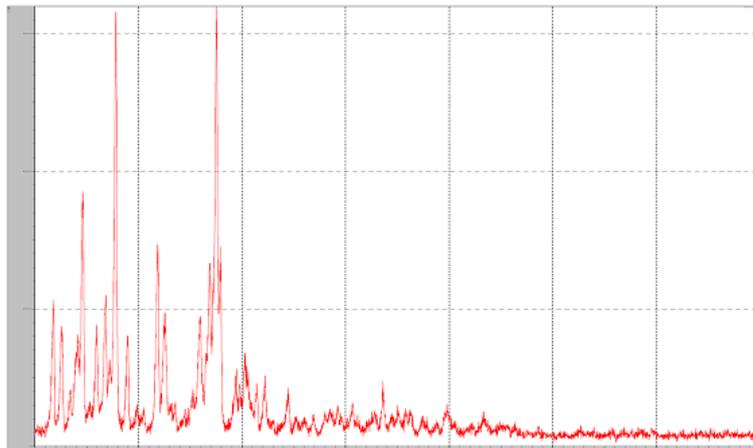


Fig. 5a: X-ray diffraction of a pure PIR powder

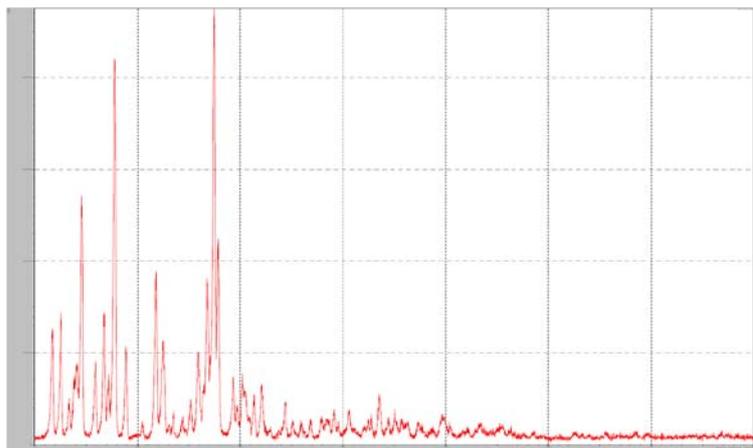


Fig. 5b: X-ray diffraction of the prepared microsp sponge (PF13)

Scanning electron microscope (SEM)

The surface of the preferable of piroxicam microsp sponge formula (PF13) was studied by scanning electron microscopy, it was shown (fig. 6) That's the fabricated microsp sponge formula have a spherical shape with sponge-like structure, the surface topography reveals that PIR microsponges contained tiny pores. The pores were induced by the diffusion of the inner phase solvent (ethanol) from the surface of the microparticles. The appearance of the particles was such that they were termed microsponges. Studying the outer surface reveal the formation of drug crystals over the particle surfaces because the optimum microsp sponge formulas prepared with higher

drug/polymer ratio (9:1). The reason behind this result is easily explained from the earlier guess-work in which at higher drug/polymer ratios, more drugs will reach the surface of the microsponges being dissolved in the solvents during diffusion.

Anyway, the presence of microchannels leads to the more penetration of dissolution medium and consequently the more dissolution rate and the better drug release. It is clear from the fig. that microsponges have a spherical shape and containing orifices. With the formation of spherical particles, it can be expected to improve powder properties of the drug, such as flowability and compressibility.

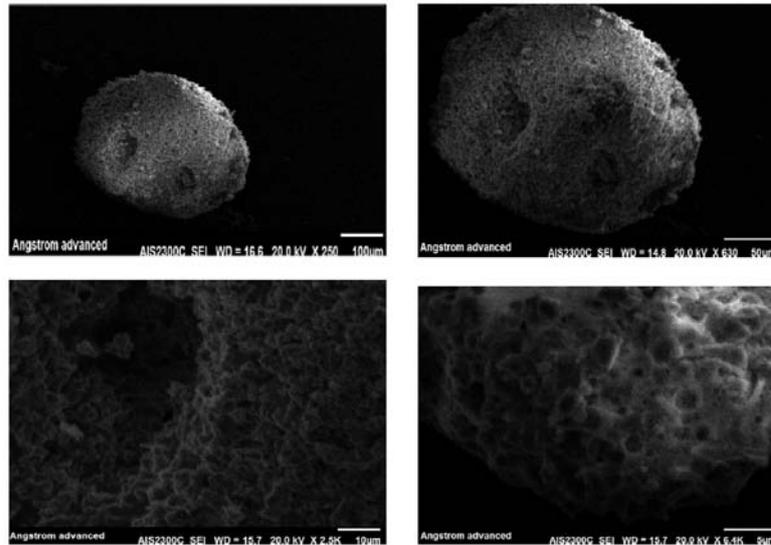


Fig. 6: Scanning electron microscope of the prepared microsp sponge (PF13)

Piroxicam microsp sponge tablet formulation

After selection of best PIR microsp sponge formula, this formula was further incorporated into a tablet dosage form using (CP, SSG) as a disintegrant, lactose as diluent and Mg stearate as a lubricating agent, and then these materials are fabricated into tablet intended to be administered orally by the direct compression method. Piroxicam microsp sponge tablets were formulated using direct compression method since it is rapid, convenient, uncomplicated, less time consuming, appropriate for the production of tablets containing sensitive moisture ingredient, less equipment used and consequently more reduction in the production cost [40]. It was assumed that the microsponges might possess a unique compression property due to their matrix or sponge-like structure which can easily be compressed by direct compression and applied by the oral route for systemic administration [41].

Variable affect on the flow properties of the tablet powder

Since the flowability of the powder mixture are important for the content uniformity of the drug in the tablet, the flow properties of the powder mixture were estimated before compression of the tablet. It is worthwhile to mention that crospovidone have a perfect Carr's index and angle of repose values when compared with the sodium starch glycolate; this may be related to the difference in the particle size, shape and its distribution [42]. Upon addition of microcrystalline cellulose (Avicel PH102) an improvement in the flow properties was showed, since it has a bigger particle size and the particle shape is more spherical. Microcrystalline cellulose (MCC) is a good excipient for direct compression processing. MCC has inherently high compactability due to its plastic deformation and limited elastic recovery. It usually provides good dispersion and uniform mixing with drugs. The results were illustrated in table (5).

Variable affect on the physical properties of the prepared tablet

The hardness parameter shows a range from (4-5.5) with no significant difference ($p > 0.05$), also the friability value are within the accepted limit, this would result in a good mechanical strength. The

disintegrants have the major function to oppose the efficiency of the tablet compactness and the physical forces that act under compression to form the tablet. An effective disintegration process is required to release the medication rapidly. Ideally, the disintegrating agent should cause the tablet to disrupt into powder particles from which the tablet was prepared. It is observed that, when CP is used as a disintegrant, tablets disintegrate rapidly within less time as compared to other tablets prepared using sodium starch glycolate. The superior disintegrating action of crospovidone is attributed to its wicking and swelling property in the presence of water. The sponge-like structure of CP is believed to contribute to its wicking action with subsequent swelling to aid disintegration. The results were shown in the table (5). The addition of CP had no adverse effect on tablet hardness, so the tablet of high hardness and rapid disintegration can be obtained by CP; however, it is important to mention that CP also maintains disintegration time of the tablet unchanged over a long period of time [43].

MCC showed excellent compact hardness, those related to the hydrogen bonding that it plays a big role in compact hardness. Hydrogen bonding is important because MCC undergoes significant plastic deformation during compression, bringing an extremely large surface area into close contact and facilitating hydrogen bond formation between the plastically deformed, adjacent cellulose particles. In addition, the existence of moisture within the porous structure of MCC acts as an internal lubricant, this facilitates slippage and flow within the individual microcrystals during plastic deformation, which enforces the formation of hydrogen bond bridges and gives better compatibility and hardness for MCC [44].

Although MCC is water insoluble material, but it has the ability to draw fluid into the tablet lattice by capillary action, the table, then swells when contact with water and hence, MCC acts as disintegrant, it is known that microcrystalline cellulose present binding and disintegrating characteristics, therefore it acts as an auxiliary tablet disintegrant because of its water-absorbing capacity [45].

Table 5: Pre and post compression parameter of PIR microsp sponge tablet and pure PIR tablet

Code	Carr index* (%)	Angle of repose*	Hardness*	Friability* (%)	Disintegration time* (min)
PF15	15.45±1.23	28.39±1.1	4.56±0.57	0.62±0.07	4.33±0.57
PF16	12.85±0.62	24.94±0.92	4.2±0.1	0.58±0.1	3.66±0.59
PF17	16.25±1.73	30.73±0.53	4.67±0.14	0.47±0.08	4.66±1.52
PF18	15.42±1.52	26.05±0.33	5.23±0.05	0.56±0.05	4.26±0.75
PF19	12.59±0.42	23.87±0.79	4.45±0.06	0.45±0.05	4.33±1.56
PF20	9.74±0.83	19.76±1.01	4.73±0.15	0.34±0.04	3.66±1.15
PF21	24.73±0.74	37.88±0.68	3.93±0.25	0.87±0.01	5.5±1.32

*All values are expressed as mean±SD

Content uniformity

All the prepared tablets had an acceptable content of PIR meeting the requirement of the USP.

In vitro dissolution studies

The release profile of the prepared PIR microsponge (PF16, PF18, PF20) and pure PIR tablet (PF21) were tested using 0.1N HCl (pH 1.2) which represents the media of the stomach where the dissolution of the prepared PIR microsponge tablets may occur. As shown in fig. (7), PF20 have the highest release value as compared with the other formulas in which it have the lowest time to provide 85% of drug release along with the maximum percent of liberated

drug in 2 min. Crospovidone demonstrated a more rapid dissolution rate for the model drugs, irrespective of their aqueous solubilities since crospovidone is a nonionic disintegrant, so no any ionic interaction occurs between it and the drug moiety, unlike the anionic disintegrants sodium starch glycolate [46]. Moreover crospovidone have particle size range (25-40) μm providing a surface area of about 1.4 m^2/gram while SSG have particle size ($\sim 50 \mu\text{m}$) with surface area about 0.2 m^2/gram , these huge difference in the surface area along with solvent like chemistry resulting in high interfacial activity that the rapid release of drug from crospovidone as compared with SSG [47]. Of fairness, we must not forget that MMC may represent the suitable additive in the case of preparing an oral tablet containing poor water soluble drug by direct compression method [48].

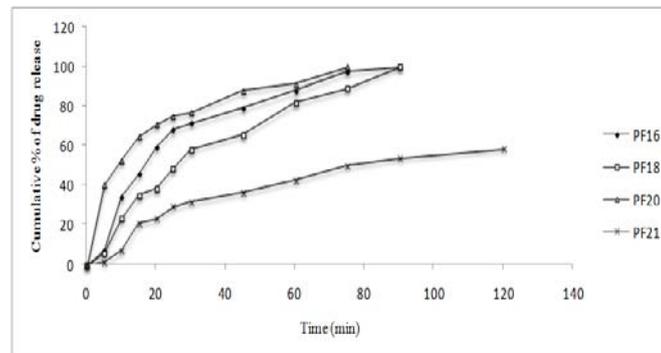


Fig. 7: Dissolution profile of prepared microsponges tablet and pure PIR tablet

Table 6: Parameter of drug release profile of PIR microsponge (PF20)

Code	Zero-order		First-order		Higuchi-model		Hixson-Crowell		Korsmeyer-pepers	
	R^2	K_0	R^2	K_1	R^2	K_H	R^2	K_s	R^2	n
PF20	0.70	0.99	0.31	-0.31	0.92	10.75	0.93	0.41	0.50	0.934

Kinetic modeling of drug release from the tablet

The releases profile of PF20 (CP4%+MMC 5%) was further studied to obtain the kinetic model of liberated PIR from the prepared formula. As shown in the table (6) the determination coefficients (R_2), the *in vitro* release data were in favor of Hixon-Crowell model. The value of n were >0.5 and <1 indicating non Fickian (anomalous) transport.

Accelerated stability studies

The degradation of PIR microsponge tablet followed first-order kinetic since a straight line resulted from the plotting the logarithm of percent drug remaining versus time. The degradation rate constant at three different temperature was estimated from the

slope of each line as mentioned in the table (7). Arrhenius plot was constructed in order to estimate the degradation rate constant (K_{25}) at 25 °C which was found to equal to $4.36 \times 10^{-4} \text{ w}^{-1}$. This value was further utilized to calculate expire date of the selected PIR microsponge tablet (PF20) by applying the following equation.

$$T_{10\%} = 0.105/K_{25}$$

Where $T_{10\%}$ is the time required for a drug to lose 10% of its potency, expire date of PIR microsponge tablet was found to be 240.54 w or about 4.6 y. The dissolution profile of the stored tablets did not show a significant change ($P > 0.05$) after 16 w. The inspection of tablets also did not reveal any layer separation, lamination, capping or any change in their physical properties.

Table 7: Degradation rate constants (K) for PIR microsponge tablets at different temperatures

Temperature (°C)	K (week ⁻¹)
40	1.612×10^{-3}
50	2.763×10^{-3}
60	7.139×10^{-3}

CONCLUSION

Piroxicam can be successfully formulated into a microsponge using quasi-solvent diffusion method, formula containing piroxicam and Eudragit RS100 in a ratio of 9:1, using ethanol as inner solvent in a volume of 5 ml and the volume of polyvinyl alcohol solution (100 ml) represent the most preferable one in which it have suitable production yield, loading efficiency and smaller particle size, the rate of dissolution are highly increased as compared with pure PIR. Furthermore, fabrication of piroxicam microsponge into tablet

dosage form by direct compression method using a crospovidone as a disintegrant along with microcrystalline cellulose have appropriate physical properties and a valuable dissolution profile, the release of piroxicam from both microsponge powder and from tablet follow Hixon-Crowell model and these formulas delivered their active ingredient by non Fickian diffusion.

So the overall result suggests that piroxicam microsponge tablet could be a promising way to enhance their solubility and dissolution profile also improvement of the unfavorable flow properties.

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CONFLICT OF INTERESTS

Declare none

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