JOURNAL OF APPLIED BIOANALYSIS, August. 2024, p. 134-142.
http://doi.org/ 10.53555/jab.v10i2.164 (ISSN 2405-710X)
Vol. 10, No. 2

OPEN ACCESS

RESEARCH ARTICLE

Solubility Enhancement Of Piroxicam Using Synthetic And Natural Hydrotropes

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Aim of the proposed research was to enhance the solubility of the drug Piroxicam by using natural and synthetic hydrotropes. Hydrotropy is a simple, effective and green platform of solubilization in which the chemical components known as hydrotropic solubilize the hydrophobic compounds in aqueous medium. Mixed hydrotropic phenomenon utilizes blends of hydrotropic agents which is taken in combination by using synthetic and natural hydrotropic agents for shows synergetic enhancement effect on solubility of poorly water soluble drugs. Piroxicam is a non steroidal anti-inflammatory drug, belonging to BCS Class II characterized by their low solubility and high permeability, which were chosen as a model drug in order to enhance its solubility by using hydrotropic technique. In this study, solubility of piroxicam was determined in individual hydrotropes as well as in different combinations of hydrotropic blend. The blends included HB 1 (sodium benzoate+ Piperazine), HB 2 (sodium benzoate+nicotinamide). These blends were taken in the ratio of 1:1, 1:2 and 1:3. And the solubility of piroxicam was determined. The HB 1 was used to prepare solid dispersion SD 1 (1:3), SD 2(1:6), SD 3 (1:9), SD 4 (1:12), SD 5 (1:15) and SD 6 (1:18) by the addition of drug in a clear solution of hydrotropic blend in water followed by its evaporation technique to produce a crystalline form. The solid dispersion were further formulated in capsules and then optimized and evaluated for dissolution, weight variation and solid state characterization by DSC and XRD.

Keywords: Hydrotropy, Solublization, BCS, Solid Dispersion, Dissolution.

INTRODUCTION

Piroxicam is chemically 4-Hydroxy-2-methyl-N-(2-pyridyl)-2H-1,2-benzothiazine-3-carboxyamid-1,1-dioxide. Piroxicam is non steroidal anti-inflammatory agent (NSAID). They are basically soluble in ethylene chloride, partially insoluble in water, and slightly soluble in ethanol. They show as analgesic and anti-inflammatory drug. The possibility to increase the aqueous solubility has an important assist for increasing the capability to overcome the adverse effects of many dosage forms. There are several perspective were introduced to improve the aqueous solvable for poor soluble dosage form example-alteration of pH, micronization, uses of surfactants, complexation, hydrotropic solubilization, mixed solvency, mixed hydrotropic solubilization. Hydrotropy called as solubilization procedure, where expansion of an addition of another solute substance, then the hydrotropic agent operator to the expansion in the fluid solvency to the first solute. Hydrotropic assign an expansion in dissolvability in water because of the nearness of enormous measure of added substances. That instrument by which they improves dissolvability are all most compressed to identified with complexation containing a powerless connection which linking the both hydrotropes operators such as sodium citrate, sodium benzoate, citric acid, and the ineffectively solvent antibiotics.The drug potency should be hardly limited by poor aqueous solubility. It said to be that the side effect of many dosage form is the result of their poor solubility. To expand it efficiency with the decreasing adverse effect of dosage form which is directly proportion to the aqueous solubility. Thus they are becomes most powerfully tools for orally, parentrally, topically administered solution. Poor bioavailability utilizes strong limits to show the dosage form by the better need to administered as much as high dose than the firm essential from the pharmacologic point of view. That can convince important adverse effects and it creates many problems which related to the

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cost of treatment. Most important parameters in pharmaceutical industries are to achieve valuable pharmacological observation is solubility with their therapeutics efficiency to the dosage form is which only gives upon the bioavailability to the contribution towards the solubility of poor drugs substances.

MATERIAL & METHODS

The UV scanning of drug was done in distilled water, pH 6.8 phosphate buffer & 0.1 M HCL. The samples were scanned in double beam UV spectrophotometer. The obtained spectrum was compared to the reference spectrum. The functional groups were determined by FTIR. The compatibility for pure drug piroxicam and their physical mixtures used in this experimental procedure was evaluated by recording of spectra using FT-IR Spectrophotometer. The spectra were recorded by taking 2mg sample in 200mg potassium bromide (KBr) and after this mixture were grounded into a fine powder. Then it was compressed into KBr pellets at 4000 Psi compaction pressure for a period of 2 min. The resolution was 1 $cm^{-1}$and the range of scanning was 400–4000 cm^{-1}.

ANALYSIS OF PIROXICAM

The analysis of Piroxicam was done in three different media using distilled water, pH 6.8 phosphate buffer & 0.1M HCl. 50 mg of Piroxicam was weighed and dissolved in 100 ml of methanol. From this solution, 10 ml will be taken and volume were dissolved in 100 ml of distilled water to produce a stock solution of 50 µg/ml. Subsequent dilutions were made to produce solutions of concentrations ranging 5-30 µg/ml .These solutions was then analyzed by double beam UV spectrophotometer at 341 nm.10 mg of Piroxicam was weighed and dissolved in 100 ml of pH 6.8 phosphate buffer to produce a stock solution of 0.1 mg/ml (100µg/ml). Subsequent dilutions were made to produce solutions of concentration ranging between 3-18 µg/ml. then solution were then analyzed by double beam UV spectrophotometer at 354 nm.. Accurately weighed quantity of piroxicam 10mg was dissolved in 100 ml of 0.1 M HCL to produce a stock solution of 0.1 mg/ml (100s µg/ml). Subsequently dilutions were made to produce solutions of concentrations ranging between 2-12 µg/ ml. These solutions were analyzed by a double beam UV spectrophotometer at 334 nm. All the experiments were performed in triplicate.

SOLUBILITY STUDIES OF PIROXICAM IN DIFFERENT MEDIA

Solubility study of piroxicam in different hydrotropic solutions was determined by using Shake flask method as mentioned in the OECD guidelines for the testing of chemicals, 1995. An excess quantity of drug piroxicam was added to 10 ml of the respective medium in a capped glass vial. The vials was kept in a magnetic stirrer in thermo stated water bath and stirred for 24 hours at 30°C. After 24 hours, equilibrium is achieved and then the solutions were transferred to centrifuge tubes and centrifuged at 2000 rpm for 5 min. The supernatant solution was separated by filtration through Whatman grade 41 filters. The filtrate thus taken and the solutions were analyzed using double beam UV spectrophotometer at 341 nm (334 nm in case of 0.1 N HCL and 354 nm in case of pH 6.8 phosphate buffers).

DETERMINATION OF EQUILIBRIUM SOLUBILITY OF PIROXICAM IN DIFFERENT COMBINATION OF HYDROTROPIC BLENDS

Two different Hydrotropes were prepared by taking different ratio of individual hydrotropes. The different ratios of hydrotropic blends are given below in the table:

Hydrotropic blends		Ratio of individual hydrotrope in hydrotropic blend		
HB 1	Sodium benzoate: Piperazine	1:1	1:2	1:3
HB 2	Nicotinamide: Piperazine	1:1	1:2	1:3

SOLID DISPERSION FORMULATION OF HYDROTROPE BLEND 1 & 2

The hydrotropic solid dispersion was prepared using various ratios of piroxicam and hydrotropic blend. The hydrotropic blend with maximum solubility enhancement ratio was selected for the preparation of hydrotropic solid dispersion and the formulations are listed in the below table:

Formulation code	Solid dispersion ratio (Drug: Hydrotropic blend)	Hydrotropic blend ratio (Sodium benzoate: piperazine)
SD 1	1:3	1:3
SD 2	1:6	1:3
SD 3	1:9	1:3
SD 4	1:12	1:3
SD 5	1:15	1:3
SD 6	1:18	1:3

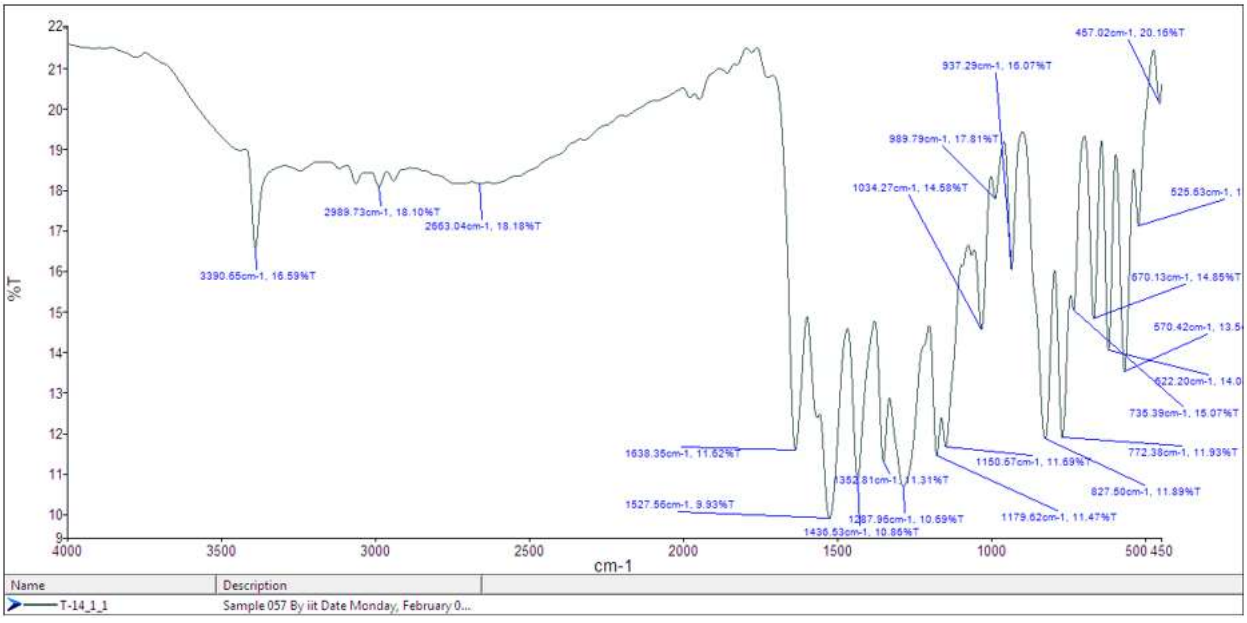
The physical mixture was prepared by taking calculated amount of piroxicam and the hydrotropes in the hydrotropic blend and intensely triturated using mortar pestle. After complete nixing, the mixture was passed through sieve number 40 and was stored in desicators until used in further investigation. The hydrotropic blend with maximum solubility enhancement ratio was selected for the preparation of physical mixture and the formulation are listed in table below:

Formulation code	Physical mixture ratio (Drug: Hydrotropic blend)	Hydrotropic blend ratio (Sodium benzoate + Piperazine)
PM 1	1:3	1:3
PM 2	1:6	1:3
PM 3	1:9	1:3
PM 4	1:12	1:3
PM 5	1:15	1:3
PM 6	1:18	1:3

The Solid Dispersion Capsules was prepared by filling of solid dispersion in capsules accurately weighed solid dispersion and transferred manually in to hard gelatin capsules which carry equal size of (00). The prepared solid dispersion and physical mixture was evaluated by determining the physiochemical properties such as production yield, drug assay, in vitro drug release of prepared hydrotropic solid dispersion**,** Fourier transform infra-red spectroscopy, differential scanning calorimetry, and powder X- ray diffraction and the prepared solid dispersion capsules was evaluated by determining weight variation and by in-vitro dissolution study.

RESULT AND DISCUSSION

The serial dilutions prepared from the stock solution of piroxicam in 0.1 M HCL, pH 6.8 phosphate buffer and distilled water were scanned in a double beam UV spectrophotometer. Calibration curves of Piroxicam were determined in distilled water, pH 6.8 phosphate buffer and 0.1 N HCL at 341 nm, 354 nm, 334 nm respectively. Standard deviation of absorbance ranged between 0.003-0.007 with the regression value of 0.992 in distilled water, 0.003-0.007 with regression value of 0.995 on pH phosphate buffer and 0.003-0.009 with the regression value of 0.993 on 0.1 N HCl. Piroxicam polymorphic forms have been reported to have different peaks for needle forms i.e. band of N-H and enolic O-H at 3385cm while the cubic form at 3330 cm. The FTIR spectrum of piroxicam has been shown in Fig.



FTIR Spectrum of Piroxicam in Infra- Red Region 4000-500cm^{-1}

The solubility was determined in different media such as distilled water.0.1 N HCl and pH 6.8 phosphate buffer and it is found that the drug (piroxicam) is partially soluble in all the mediums.

Various hydrotropic blends were prepared using sodium benzoate, piperazine and nicotinamide. The blends included HB 1 (sodium benzoate +

piperazine), HB 2 (sodium benzoate + nicotinamide). These blends were taken in the ratio of 1:1. 1:2 and 1:3 and the solubility of piroxicam were determined. Six different formulations of piroxicam solid dispersion (SD 1, SD 2,SD 3, SD 4, SD 5 and SD 6) were prepared in the ratio 1:3, 1:6, 1:9, 1:12, 1:15 and 1:18 respectively using the hydrotropic blend sodium benzoate: piperazine (1:3).

Three different formulations of piroxicam physical mixture (PM 1, PM 2, PM 3 PM 4, PM 5 and PM 6) were prepared in the ratio 1:3, 1:6, 1:9, 1:12, 1:15 and 1:18 respectively using the hydrotropic blend sodium benzoate: piperazine (1:3) and accurately weighed drug . Three different formulations of piroxicam physical mixture (PM 1, PM 2, PM 3 PM 4, PM 5 and PM 6) were prepared in the ratio 1:3, 1:6, 1:9, 1:12, 1:15 and 1:18 respectively using the hydrotropic blend sodium benzoate: piperazine (1:3).

Physicochemical Evaluation: The evaluation of hydrotropic solid dispersion by done by determining the following parameters:

The production yield

The values of the production yield of the formulations of prepared solid dispersion before sieving were ranged from 90-99%. Satisfactory reproducibility of result was obtained on repetition and has been enlisted in table below:

Production Yield of the Prepared Hydrotropic Solid Dispersion

Formulation code	Average production yield (%±SD)
SD 1	86.80%±0.0004
SD 2	70.93%±0.0003
SD 3	78.81%±0.0001
SD 4	75.33%±0.0001
SD 5	88.23%±0.0004
SD 6	92.67%±0.0003

Drug assay

The values of the drug content of the six formulations of piroxicam solid dispersion were determined and have been enlisted in table below:

Drug Content of the Prepared Hydrotropic Solid Dispersion

Formulation code	Average drug content (mg±SD)	Estimated drug content (mg)
SD 1	6.6521±0.11	15.742
SD 2	7.6852±0.12	22.691
SD 3	10.5321±0.109	30.251
SD 4	12.65321±0.06	60.01
SD 5	15.321±0.15	72.533
SD 6	19.2235±0.08	80.65

Fourier Transform Infra-red Spectroscopy

It is found that, the O-H stretching vibration of pure piroxicam appeared at 3338.18 cm^{-1} as a broad peak while N-H appeared at 3253.91 $cm^{-1.}$ The FTIR of hydrotropic solid dispersion (SD 1, SD 2, SD 3) showed the broad peaks for O-H at 3460 .64 cm^{-1}, 3443.32 cm^{-1} and 3442.37 cm^{-1} respectively, and the peaks for N-H at 3354.57 cm^{-1}, 3346.85 cm^{-1} and 3339.14 $cm^{-1.}$

This indicates that the physical mixture spectra were only the summation of piroxicam solid dispersion. This indicates that there is no interaction between piroxicam, sodium benzoate and piperazine.

Differential Scanning Calorimetry (DSC)

The differential scanning calorimetric studies carried out in the order to detect the possible polymorphic transitions that might have occurred during the preparation of hydrotropic solid dispersion. The DSC curves obtained for pure piroxicam and hydrotropic solid dispersion of piroxicam (SD 1, SD 2, and SD 3) in different ratios.

The pure piroxicam had ash endothermic peak at 201°C, which corresponds to the melting points of piroxicam. The endothermic peak for the hydrotropic solid dispersion SD 1 were found at 207° C and 210° C , for SD 2 at 207° C and 209° C-, for SD 3 at 204°C. These values are very close to the melting point of hydrotropes used i.e.>300°C for sodium benzoate and piperazine. The areas and the sharpness of the peaks were decreased, which indicates that the crystalline of the drugs was reduced and it might be converted into amorphous form.

This indicated that DSC thermogram of SD 1 shows Distinctive peaks which indicates that the drugs was less soluble in the hydrotropic blends, where as SD 2 shows less area of peaks and SD 3 showed least of

area sharpness of the peaks indicating more solubility of drugs in the hydrotropic blends. Thus it may be concluded that an increase the concentration of the hydrotropic leads to an increase in the solubility of the drug.

X-Ray diffraction (XRD)

In the XRD study, the intense and sharp peaks have been found that indicates the pure drug was crystalline in nature. The XRD studies of the hydrotropic solid dispersion SD 2 shown peaks at 2θ at 9.542°, 14.421°, 22.255° 15.401° and where as SD 3 showed peaks 9.560°, 16.852°, 23.573° and 29.705°. The reduction in the number and the intensity of the peaks in the diffractogram indicated reduction in the crystalline nature of the drugs and it might have converted to amorphous form.

It may be concluded that the peak of SD 2 are more intense due to the crystalline diffraction pattern of piroxicam. Since more mount of the drug has solubilised in SD 3 thus the number of peaks reduced and the reduction in intensity indicates that SD has changed to amorphous form more than SD.

The physical mixture of piroxicam was evaluated by the following parameters:

Drug assay

The values of the drug content of the six formulations of piroxicam physical mixture were determined. Drug Content of the Prepared Physical Mixture is mentioned below:

Drug Content of the Prepared Physical Mixture

Formulation code	Average drug content (mg±SD)
PM 1	8.36±0.006
PM 2	11.30±0.002
PM 3	13.48±0.003
PM 4	15.92±0.004
PM 5	17.62±0.005
PM 6	24.3±0.012

Fourier Transform Infra-red spectroscopy

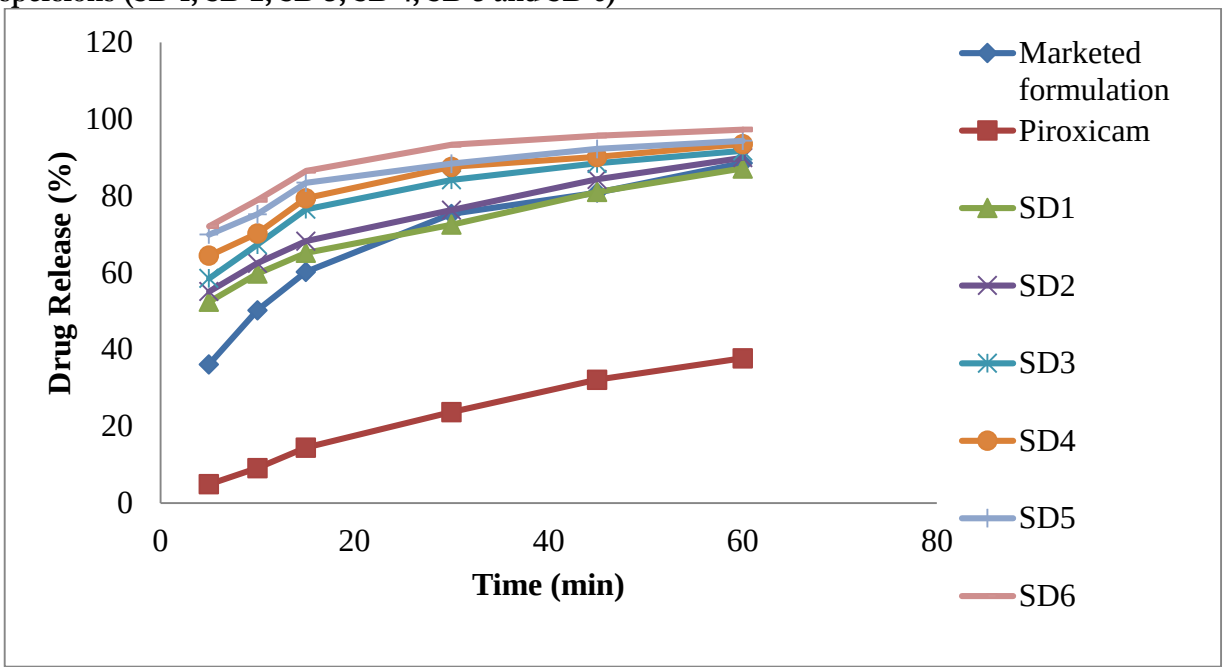
It is found that the 0-H stretching vibration of pure piroxicam appeared at 3338.18 cm^{-1} as a broad peak while N-H appeared at 3253.91 cm^{-1}. The FTIR of the physical mixture (PM 1, PM 2 and PM 3) showed the broad peaks for O-H at 327.83cm_{-1}, 3275.81cm^{-1}, 3277.82cm-^{1} respectively, and the peaks for N-H at 3337.16 cm^{-1}, 3337.17 cm^{-1} and 3338.15 cm^{-1} This indicates that there is no interaction between piroxicam, sodium benzoate and piperazine.

In-vitro Dissolution Studies

Comparison between in vitro dissolution studies of pure piroxicam, marketed formulation and prepared solid dispersion formulations

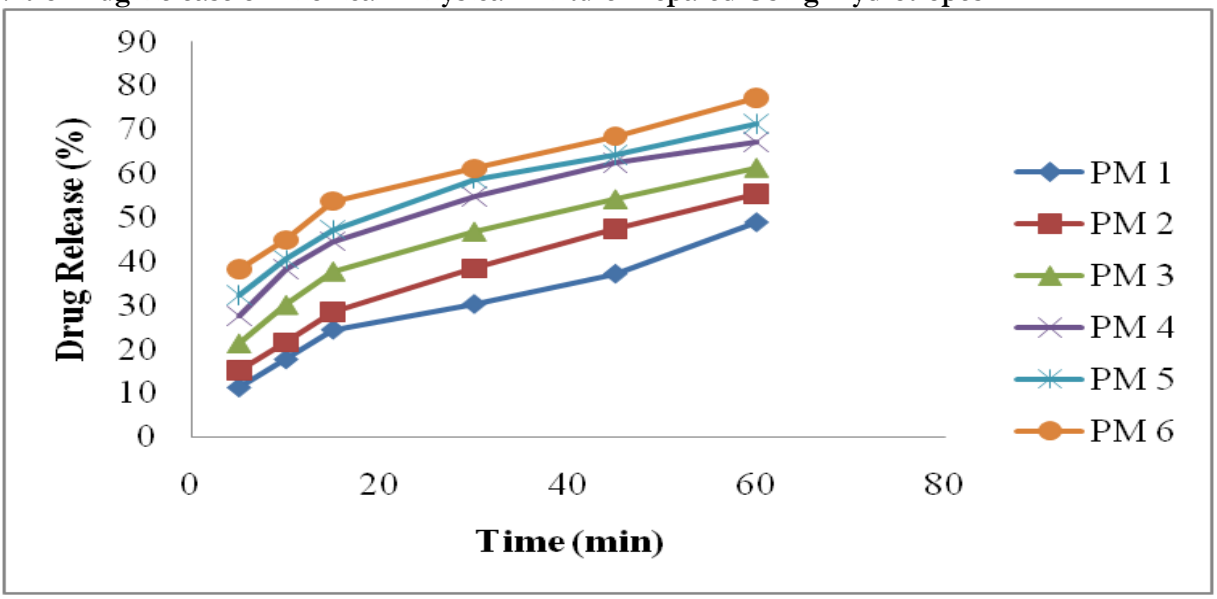
The cumulative drug release of the pure drug, marketed formulation (Pirox 20 mg) and prepared solid dispersion formulations have been studied. After 45 minutes, the release of marketed formulation (Pirox 20 mg) was found to be 80.84% approx, 81.03% for SD 1, 84.32% for SD 2, 88.49% for SD 3, 90.13% for SD 4, 92.21% for SD 5 and 95.69% for SD 6 where as the release from the pure piroxicam was 32.12% approx. After the comparison of the cumulative drug release values of the marketed formulation and pure piroxicam, it was concluded that after 20 minutes approx 78% of the marketed formulation has been released compared to just 21% of the pure piroxicam. This is due to the fact of piroxicam belongs to BCS Class II, having low solubility and high permeability characteristic. Upon its oral administration it takes 3 to 5 hours for piroxicam reaches to the peak plasma concentration due to which its drug release is poor, where as pirox is a marketed formulation, which would have been manufactured using improved solubility and dissolution enhancement methods.

Comparative Dissolution Profiles of Marketed Formulation Pirox (20mg) Pure Piroxicam and Solid Dispersions (SD 1, SD 2, SD 3, SD 4, SD 5 and SD 6)



The in vitro drug release of the prepared piroxicam physical mixture formulations PM 1, PM 2, PM 3, PM 4, PM 5 and PM 6, using the hydrotropic blend of sodium benzoate and piperazine (1:3) in the ratios of 1:3, 1:6, 1:9, 1:12, 1:15 and 1:18 respectively. The influence of the hydrotropic on the solubility and dissolution of piroxicam was studied on the in vitro release of piroxicam. The six formulations, PM 1, PM 2, PM 3, PM 4, PM 5 and PM 6 released 77.30% of piroxicam where as PM 4 and PM 5 released approx 67.20-71.40%. This concluded that the best result which obtained from PM 6> PM 5> PM 4. The graph is shown below:

In Vitro Drug Release of Piroxicam Physical Mixture Prepared Using Hydrotropes

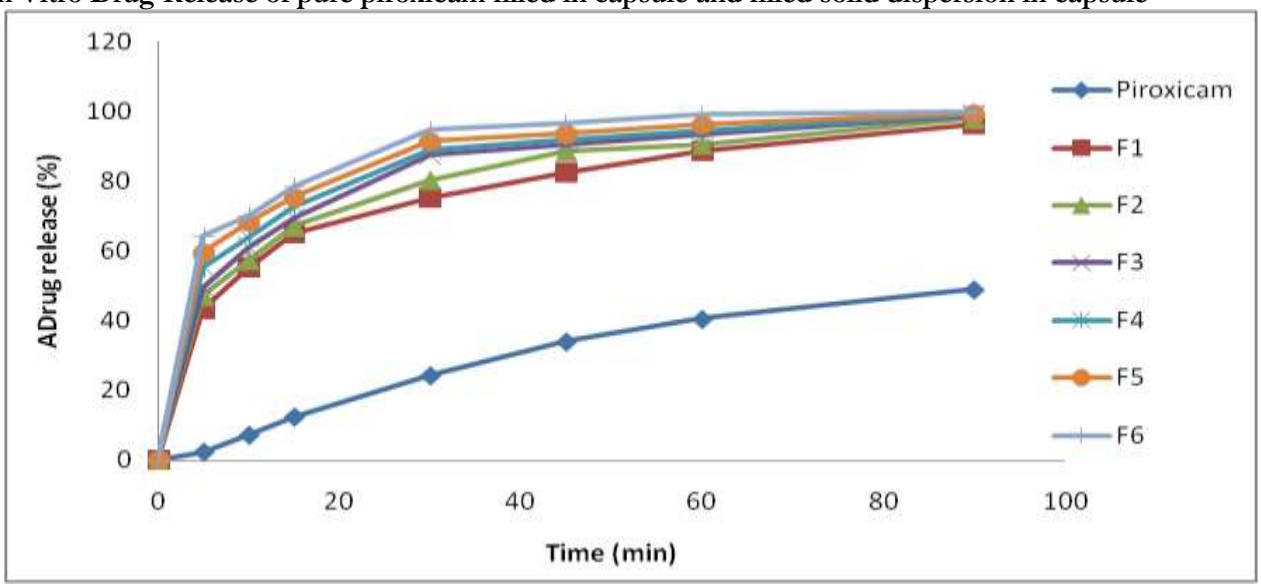


The comparison between the in vitro drug releases of the prepared solid dispersion which was filled in capsules and the pure piroxicam capsules. The solid dispersion formulations were prepared by using hydrotropic blend HB 1 (sodium benzoate+ piperazine) in the ratio 1:3. The effect of hydrotropic blend on the in vitro release of solid dispersion capsules were select as 3 best release formulation and with filled piroxicam capsule which formulation were studies.

The comparison that the release profile of the pure piroxicam is less as to that compared to that solid dispersion. Amongst all the formulations, pure piroxicam showed least release where as Formulation 6 showed highest release. This indicated that the

release profile was obtained as: Formulation 6.> Formulation 5> Formulation 4> pure piroxicam.

In Vitro Drug Release of pure piroxicam filled in capsule and filled solid dispersion in capsule



CONCLUSION

The standard calibration curves were prepared at 0.1 M HCL, Ph 6.8 phosphate buffer and distilled water. The serial dilutions prepared from the stock solution of piroxicam in 0.1 M HCL, pH 6.8 phosphate buffer and distilled water were scanned in a UV visible double beam spectrophotometer. The λ_{max} were 334 nm for 0.1 M HCL, 354 nm for pH 6.8 phosphate buffer and 341 nm for distilled water which is close to 333 nm for 0.1 M HCL and 354 nm for pH 6.8 phosphate buffer and 375 nm for distilled water. Standard deviation of absorbance ranged between 0.003-0.009 with a regression value of 0.993 in HCL, 0.003-0.007 with a regression value of 0.995 at pH 6.8 phosphate buffer, 0.003-0.007 with a regression value of 0.993 in distilled water. It confirmed that the drug was pure. The FTIR scanning showed no incompatibility between the drug and the hydrotropes. The UV interference study was accepted out in order to select a hydrotropes which would not interfere in UV spectrophotometric estimation of piroxicam . The solubility studies of piroxicam were perform in different medium, individual hydrotropes and in hydrotropic blends in order to determine the blend which would enhance the solubility of piroxicam to the maximum extent. Various hydrotropic blends were prepared using sodium benzoate, piperazine and nicotinamide. The blends included HB 1 (sodium benzoate + piperazine), HB 2 (sodium benzoate + nicotinamide). These blends were taken in the ratio of 1:1. 1:2 and 1:3 and the solubility of piroxicam were determined. The results concluded that HB 1 was the best amongst them and thus was selected for the formulation of solid dispersion. It was also kept in mind to take safe dose of both hydrotropic agents which follows as sodium benzoate safe dose lies between 5mg/kg. And piperazine lays safe dose for adults 1 to 2 grams daily. It was found that all the formulations contains safe dose of both hydrotropes. The hydrotropic solid dispersions of piroxicam were prepared using hydrotropic technique. The hydrotropic blend of sodium benzoate: piperazine (1:3) was preferred for the preparation of solid dispersion with six formulations in different ratios, i.e. SD 1(1:3), SD 2(1:6), SD 3(1:9), SD 4 (1:12), SD 5(1:15) and SD 6(1:18) were prepared. The physical mixtures (PM 1, PM 2, PM 3, PM 4, PM 5 and PM 6) were ready in the same manner. The physicochemical evaluation concluded that the values of production yield of the three formulations of the solid dispersions before sieving ranged from 90-99%. The drug content of SD 1 was 6.6521 mg ± 0.11, SD 2 was 7.6852 mg ±0.12, SD 3 was 10.5321 mg ±0.109, SD 4 was 12.6532 mg ±0.06, SD 5 was15.321 mg ±0.15 and SD 6 was 19.2235 mg±0.08.1 was mg 6.6521 ±0.11

The preparation of solid dispersion of piroxicam using sodium benzoate and piperazine has been definite by FTIR, DSC and XRD study. The physicochemical evaluation parameters concluded that there was a decrease in crystalline nature of dosage form where it might have changed to amorphous form. The in vitro drug release study showed where the solid dispersions organized use in combination of hydrotropes one natural hydrotropes and synthetic hydrotropes showed enhanced dissolutions. The pure piroxicam released about 32.12%, compared to that of the SD 1 81.03%, SD 2 84.32%.SD 3 88.49%, SD 4 90.13% SD 5 92.21% and SD 6 95.69%. The drug release of physical

mixtures showed was found to be PM 4.(67.20%), PM 5(71.40%) and PM 6(77.30%).

The solubility studies data shows that the hydrotropic blend HB 1 enhanced the solubility to the highest extent as compared to HB 1 and HB 2. The solubility enhancement ratio of HB 1 (sodium benzoate: piperazine) in the ratio 1:3 shows maximum solubility enhancement of up to 85.92 times as compared to that of pure drug.

After conducting these studies, it may be conducted that SD 6 is the best formulation amongst all the six formulations because it release maximum drug. This indicates that an enhancement in the concentration of hydrotropes leads to an increase in the solubility of poor water soluble dosage form. On their basis of safe dosage we formulated the best formulation. the solubility enhancement ratio of HB 1(sodium benzoate: piperazine) in the ratio 1:3 shows maximum solubility enhancement of up to 85.92 times as compare to that pure dosage form. The use of high amount of synthetic hydrotropes is very dangerous for human administration. There were moderately some works done since the introduction of hydrotropy to discover in details with the systematic way in ability to natural hydrotropy to enhance the evident solubility of drug. This research work was give insight to use the natural hydrotropes in solubility enhancement as well as formulation development. Natural hydrotropes can be used in combination of synthetic hydrotropes and this reduces the concentration of individual hydrotropes using mixed hydrotropy approach.

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