



ENHANCEMENT OF SOLUBILITY AND DISSOLUTION RATE OF POORLY WATER SOLUBLE DRUG BY SPRAY DRYING USING DIFFERENT GRADE OF CHITOSAN

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ABSTRACT

Piroxicam is a Non-steroidal anti-inflammatory, analgesic and anti-pyretic drug which is widely used in Muscle-skeletal disorder like osteoarthritis. Piroxicam has bad taste, half life of 30 hrs and poor water solubility. So the present work was focused on prepare the microspheres to improve solubility and dissolution of piroxicam using two grade of chitosan with different drug: polymer ratio by spray-drying technique. The effect of different polymers and drug-polymer ratios on solubility and dissolution of microspheres was investigated. The prepared microspheres were characterized by Fourier transform infrared spectroscopy, Differential scanning calorimetric, XRD study and scanning electron microscopy, Drug loading and drug-release properties. Spray dried microspheres of exhibited decreased crystallinity. The solubility and dissolution of the Spray dried microspheres of both the polymers with different ratio were improved compared with pure sample of piroxicam. Hence this spray drying technique can be used for formulation of tablets of piroxicam by direct compression with directly compressible tablet excipients.

Keywords: Microspheres; Spray drying; Piroxicam, Solubility, Dissolution.

INTRODUCTION

Formulation and manufacture of solid oral dosage forms, and tablets in particular, have undergone rapid change and development over the last several decades. One of the most revolutionary technologies is that of direct compression. Direct compression is economical, facilitates processing without the need of moisture, heat and involves small number of processing steps. In direct tableting method, it is necessary to increase flowability and compressibility of the bulk powder in order to retain a steady supply of powder mixture to the tableting machine and sufficient mechanical strength of the compacted tablets. In addition to increasing efficiency of the manufacturing process it is also important to increase bioavailability of the drug by improving the solubility of the bulk drug powder. Thus, one of the major challenges to drug development today is poor solubility, as an estimated 40% of all newly developed drugs are poorly soluble or insoluble in water¹. As a result, much research has been conducted into methods of improving drug solubility and dissolution rates to increase the oral bioavailability of hydrophobic drugs.

Consequently, many hydrophobic drugs show erratic and incomplete absorption from the gastrointestinal tract of animals and humans, which may lead to therapeutic failure. Thus, one of the major challenges to drug development today is poor solubility, as an estimated 40% of all newly developed drugs are poorly soluble or insoluble in water^{2, 3, 5, 6}. As a result, much research has been conducted into methods of improving drug solubility and dissolution rates to increase the oral bioavailability of hydrophobic drugs. Various techniques such as melt adsorption, supercritical fluid processes, using different composition of solvents to prepared the microspheres to improve the dissolution rate of poorly water soluble drugs. And amorphous state to improve their dissolution. Manipulation of the solid state by decreasing crystallinity of drug substances through formation of solid dispersion is one of the methods used for promoting drug dissolution. The solid dispersion technique has often proved to be the most successful in improving the dissolution and bioavailability of poorly water soluble active pharmaceutical ingredients because it is simple, economic, and advantageous technique. The concept of solid dispersion covers a wide range of systems. The enhancement in the dissolution rate is obtained by one or a combination of the following mechanisms: eutectic formation, increased surface area of the drug due to precipitation in the carrier, formation of true solid solution, improved wettability, and drug precipitation as a metastable crystalline form or a decrease in substance crystallinity. The type of solid dispersion formed depends on both the carrier-drug

combination and the method of manufacture. Microwaves irradiation was used recently for the preparation of solvent-free solid dispersions and for enhancement of release of the poorly soluble drug. Spray drying is one such technique of preparing solid dispersion and is widely used as an alternative to milling to reduce particle size. Spray chilling or spray congealing is another form of solid dispersion where the melted mass is atomized into droplets, which quickly solidify in a cool air⁷. The advantage in spray chilling is that no additional manufacturing step is needed to pulverize the solid dispersion. In pharmacy, spray chilling has been used to prepare sustained-release formulations, to improve stability^{8, 9, 10}. The technique also has the advantages of being free from organic solvents compared to spray drying. The method has also been used by the food industry, for example, to encapsulate vitamins and mineral. Piroxicam was chosen as a poorly water soluble drug. Piroxicam is N-2-(3-xylylanthranilic acid is one of the safest and most potent non-steroidal anti-inflammatory drugs being widely used in the market. The drug used to treat rheumatoid arthritis, osteoarthritis, and mild to moderate pain. It has low aqueous solubility and hence poor dissolution. The present investigation is aimed at use of polymers as improve solubility and dissolution like low molecular Chitosan and high molecular Chitosan are used to prepare microspheres. Chitosan is a (Low (Low molecular weight (150,000) chitosan is 75-85 percent deacetylated and has a viscosity of 20-200 cps) / high (High molecular weight (600,000). the present work was conducted to improve the solubility and dissolution of piroxicam using polymer by spray drying techniques.

MATERIALS AND METHOD

Piroxicam (PIRX) and low molecular weight chitosan (L.M.C) & high molecule weight chitosan (H.M.C) were gifted by IPCA lab, Mumbai, (India). The other chemicals and reagents used were of AR grade.

Preparation of microspheres

The microspheres were prepared by spray-drying technique. The spray drying was performed by Mini Spray Dryer LSD -48; (Jay instrument & systems Pvt. Ltd. Mumbai). The different drug-polymer ratios used for various microsphere formulations were prepared described in Table 1. The polymer solution was prepared by adding given quantity of polymer to the solvent. For low molecular Chitosan and high molecular chitosan 1% glacial acetic acid and water were used as solvent mixture. The given quantity of piroxicam was added to the polymer solution and the resulting mixture was spray-dried. The spray drying parameters are described in Table 2.

Table 1: Shows formulation of microspheres

Polymer	Drug-polymer ratio				
	F1	F2	F3	F4	F5
L.M.C microspheres	1:0.5	1:1	1:1.5	1:2	1:2.5
H.M.C microspheres	F6	F7	F8	F9	F10
	1:0.5	1:1	1:1.5	1:2	1:2.5

Table 2: Shows spray-drying parameters

Polymer	Inlet temperature (°C)	Feed pump speed %	Vacuum (mm Wc)	Aspirator level (kg/cm ²)
L.M.C microspheres	140	20	-65	2
H.M.C microspheres	140	20	-65	2

Evaluation of microspheres

Determination of percentage yield

The yield of microspheres was determined by the formula,

$$\% \text{Yield} = \frac{\text{Total Weight of Microspheres}}{\text{Total Weight of Raw Material}} \times 100$$

Total Weight of Raw Material

Determination of drug loading

The drug loading was determined by UV-Visible spectrophotometer. The microspheres were stirred with 100 ml pH 7.4 phosphate buffer for 2 h. The drug concentration was determined at 332 nm after suitable dilution. The readings were taken in triplicate.

Determination of solubility studies

The solubility of piroxicam microspheres in water and pH 7.4 phosphate buffer was determined by taking excess quantity of microspheres in 50 ml to screw-capped glass vials filled with water. The vials were shaken for two hours on mechanical shaker. The solution was filtered through Whatmann filter paper No.1 and drug concentration was determined at 332 nm.

Differential scanning calorimeter (DSC)

DSC study was carried out to detect possible polymorphic transition during the crystallization process. DSC measurements were performed on a DSC DuPont 9900, differential scanning calorimeter with a thermal analyzer.

Fourier transforms infrared (FTIR) spectroscopy

The FTIR spectral measurements were taken at ambient temperature using a Shimadzu, Model 8033 (USA). Samples were dispersed in KBr powder and the pellets were made by applying 5 ton pressure. FTIR spectra were obtained by powder diffuse reflectance on FTIR spectrophotometer.

X-ray diffraction analysis

X-Ray powder diffraction patterns were obtained at room temperature using a Philips X' Pert MPD diffractometer, with Cu as anode material and graphite mono chromator, operated at a voltage of 40 mA, 45 kV. The process parameters used were set as scan step size of 0.0170 (2θ).

Scanning electron microscopy (SEM) study

Scanning electron microscopic (Joel- LV-5600, USA, with magnification of 250x) photographs were obtained to identify and confirm spherical nature and Surface topography of the crystals.

Dissolution studies of microparticles

The dissolution of piroxicam pure sample, spray dried microspheres formulations were determined by using USP dissolution apparatus XXIV-Type II (Electro Lab, Mumbai). Dissolution medium was 900 ml 7.4 Phosphate buffer. The amount of dissolved drug was determined using UV spectrophotometric method (UV 1601 A Shimadzu, Japan) at 332 nm. The readings were taken in triplicate.

RESULTS AND DISCUSSION

The glass transition temperature (T_g) is the second-order phase change temperature at which a solid glass is transformed to a liquid-like rubber. As the temperature increases above, T_g various changes, such as increase of free volume, decrease of viscosity, increase of specific heat, and increase of thermal expansion, are noticed. During spray drying, if the drying temperature exceeds the T_g of the polymer, the powder becomes soft or sticky while still warm. This causes sticking of the powder to the side walls of drying chamber. The T_g of low and high molecular weight of Chitosan is between 152- 203°C, Therefore, water and 1% glacial acetic acid were used as solvent for Low and High molecular weight Chitosan microspheres.

The drug loading and % yield of different formulations of piroxicam with chitosan (Low and high molecular chitosan). Result showed in Table 3.

In the solubility studies of the prepared microspheres with low molecular chitosan, F-4 microspheres showed highest solubility of drug in both water (0.081 mg/ml) and pH 7.4 (0.128 mg/ml) in comparison with pure drug (water: 0.013 mg/ml; pH 7.4: 0.054 mg/ml) and microspheres prepared with high molecular chitosan, F-8 microspheres showed highest solubility of drug in both water (0.072 mg/ml) and pH 7.4 (0.104 mg/ml) in comparison with pure drug (water: 0.013 mg/ml; pH 7.4: 0.054 mg/ml). In addition, as the concentration of chitosan increased in the formulation, the solubility gradually increased up to a certain concentration followed by decrease in the solubility, however the variability in the solubility. Different solubility if formulations showed in Table 3.

Table 3: shows different evaluation of microspheres

Microspheres	Formulations number	% Yield	%Drug loading	Solubility in water(mg/ml)	Solubility in pH7.4(mg/ml)
Pure drug	0.013	0.054			
L.M.C microspheres	F1	43.56	47.02±0.04	0.057 ± 0.004	0.077± 0.01
	F2	58.29	54.26±0.21	0.071± 0.002	0.086± 0.011
	F3	40.57	59.47±0.24	0.076± 0.010	0.103± 0.005
	F4	49.36	57.98±0.52	0.081± 0.007	0.128± 0.002
	F5	57.09	63.27±0.32	0.063± 0.011	0.079± 0.022
H.M.C microspheres	F6	47.83	79.38±0.03	0.047± 0.001	0.065± 0.001
	F7	45.37	83.83±0.01	0.059± 0.003	0.086± 0.021
	F8	42.32	87.49±0.17	0.072± 0.004	0.104± 0.002
	F9	58.93	79.54±0.10	0.055± 0.001	0.078± 0.005
	F10	61.72	86.37±0.25	0.047± 0.013	0.063± 0.008

The DSC thermogram (fig. 1) shows a sharp endothermic peak for all the piroxicam. This one step melt might be due to only one crystal form (Triclinic) of the piroxicam formed during the spray dried process, thus indicating that piroxicam did not undergo any crystal modification during microspheres processes. The temperature range of the endothermic peak of all the piroxicam crystals lies in the range of 199-202°. Melting points show slight variation as the nature of the crystals might have been affected by the solvent or polymer. In DSC study chitosan (both high and low molecular weight) did not affect the DSC spectrum of piroxicam, thus there is no change in physical properties of piroxicam.

The FTIR spectrum of drug, polymer, drug and different drug: polymer ratio (PIRX: L.M.C, PIRX: H.M.C) microspheres are showed in Fig 2. The PIRX exhibited characteristic peaks in all the spectra's like -NH and -OH stretching which ties at 1385 cm^{-1} , 1635 or 1625 cm^{-1} (N-H-CO₃ stretching vibration), 1525 cm^{-1} (secondary -NH₂ stretching), 1440 cm^{-1} (CH₃ AND Ar-c=c stretching), 1355 cm^{-1} (sym. -CH₃) and 1155 and 1070 cm^{-1} or 1050-1070 cm^{-1} (-SO₂-N-) 770 and 740 or 740 cm^{-1} (Ortho disubstituted phenyl). The Low molecular weight chitosan microspheres exhibited both the characteristic peaks of PIRX at 1385 and 1635 cm^{-1} . high molecular weight Chitosan microspheres

depicted no shift in both the characteristic peaks of PIRX.. The results of IR spectroscopy reveal that there was no chemical interaction between drug and the polymer.

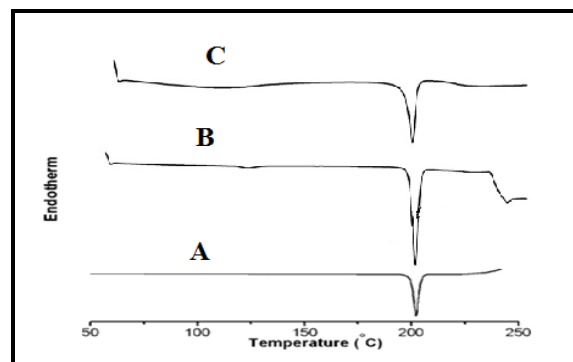


Fig. 1: it shows DSC spectra of A) pure piroxicam, B) Microspheres with low molecular weight chitosan, C) Microspheres with high molecular weight chitosan

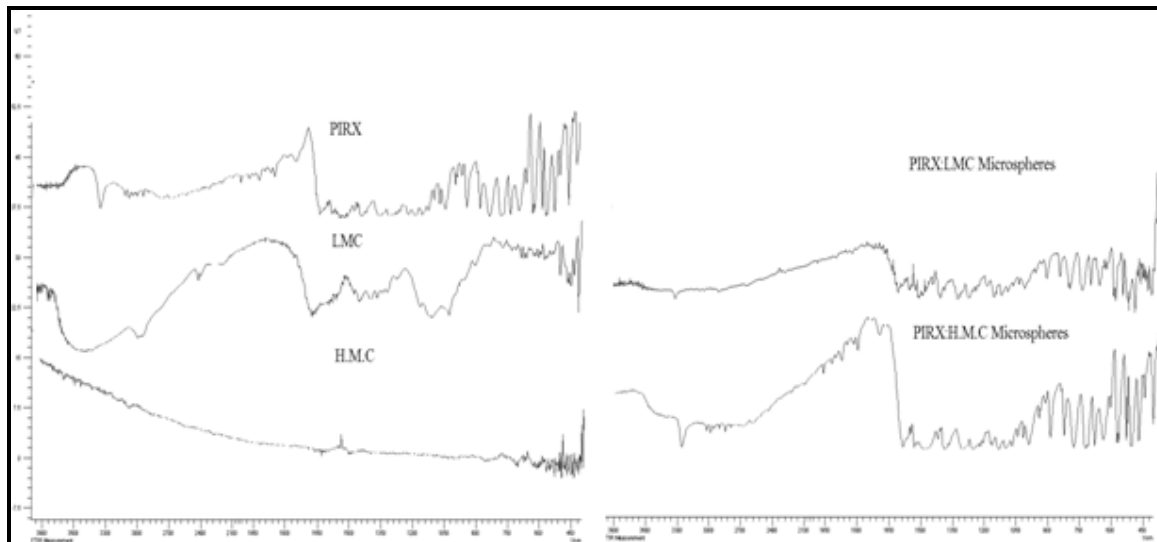


Fig. 2: it shows FTIR spectra of drug, polymers, drug-polymer microspheres

All the samples showed similar peak positions (2θ) in X-ray diffraction, formation of different polymorphs of piroxicam was ruled out. However relative intensities of XRD peaks were modified (fig. 3). This could be attributed to the markedly different crystal habits of the samples. Therefore the relative abundance of the planes exposed to the X-ray source would have been altered, producing the variations in the relative intensities of the peak or may be due to differences in particle sizes.

The SEM micrographs of A) Pure piroxicam B) low molecular weight chitosan Microspheres C) high molecular weight Chitosan Microspheres are showed in Fig. 4. Size of pure drug was found to be 8-17 μm and they were irregular size. The microspheres prepared by spray drying were spherical in shape with small diameter in the range 4-11 μm . The SEM images confirmed the uniformity and fine nature of the microspheres which contributed for rapid drug release from the microspheres.

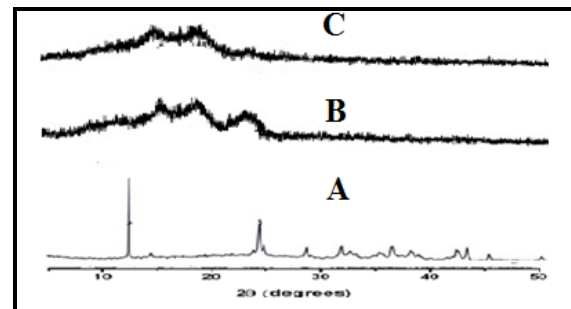


Fig. 3: it shows XRD spectra of A) pure piroxicam, B) Microspheres with low molecular weight chitosan, C) Microspheres with high molecular weight chitosan

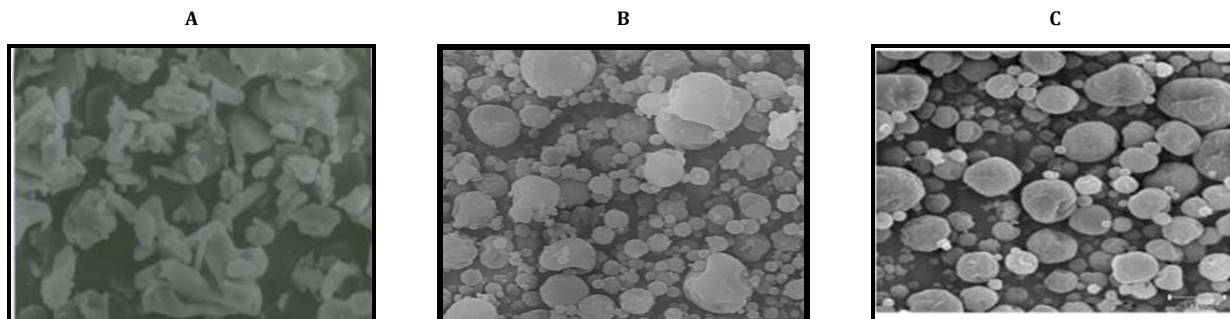


Fig. 4: it shows SEM of A) pure piroxicam, B) Microspheres with low molecular weight chitosan, C) Microspheres with high molecular weight chitosan

The dissolution profiles of piroxicam (fig. 5 & 6) exhibited improved dissolution behavior for both low and high molecular weight chitosan microspheres than pure sample. The formulation F3 & F10 showed higher dissolution compare to all the formulation. The reason for this faster dissolution could be linked to the better wettability of the Microspheres. The amount of drug dissolved in 60 min greatly varied for microspheres.

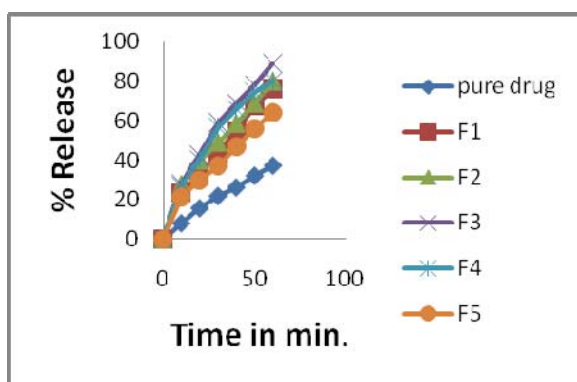


Fig. 5: it shows In vitro drug release from low molecular weight chitosan microspheres

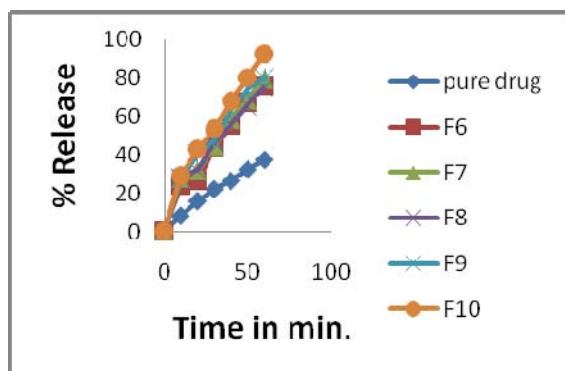


Fig. 6: it shows In vitro drug release from high molecular weight chitosan microspheres

CONCLUSION

Spray dried microspheres of piroxicam containing different ratio of low and high molecular weight chitosan prepared by spray drying

technique. Spray dried microspheres exhibited decreased crystallinity and improved micromeritic properties. DSC and XRD studies showed that there is no change in the crystal structure of piroxicam during the spray drying process. The solubility and dissolution of all the prepared microspheres showed high solubility and high% release compared to pure sample of piroxicam. Hence spray drying technique is a good method to improve solubility and dissolution of poorly water soluble drug using different polymers. Hence these prepared microspheres can be used for formulation of tablets of piroxicam by direct compression without further process like (mixing, granulation) with directly compressible tablet excipients.

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