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USE OF SPRAY DRIED MICROSPHERES TECHNIQUE TO ENHANCE SOLUBILITY OF POORLY SOLUBLE DRUG

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ABSTRACT

Chlordiazepoxide, a member of the 1, 4-benzodiazepine, showing poor aqueous solubility and dissolution rate in water, so the present work was focused to prepare the microspheres of Chlordiazepoxide to improve its solubility and dissolution; using chitosan with different drug: polymer ratio by spray-drying technique. The effect of different drug: polymer ratio on the solubility and dissolution of microspheres was investigated. The prepared microspheres were characterized by Fourier transform infrared spectroscopy, Differential scanning colorimetry, XRD, Scanning electron microscopy, drug loading and drug-release properties. Spray dried microspheres exhibited decreased crystalline characteristics, higher solubility and dissolution compared with the pure sample of Chlordiazepoxide. Hence this spray drying technique can be used for the formulation purpose of Chlordiazepoxide to increase solubility & dissolution of the drug.

Keywords: Chlordiazepoxide, dissolution, microspheres, spray-drying.

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INTRODUCTION:

Formulation and manufacturing of solid oral dosage forms and tablets in particular, have undergone rapid change and development over the last several decades; to increase efficiency of the manufacturing process it is important to increase bioavailability of the drug by improving the solubility of drug. 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. As a result, many researchers have been worked to improve drug solubility and dissolution rates for increasing oral bioavailability of hydrophobic drugs [1, 2, 3, 4, 5]. Manipulation of the solid state by decreasing crystallinity of drug substances through formation of solid dispersion is useful method used for promoting drug dissolution [6]. Recently microwaves irradiation has been employed for the preparation of solvent-free solid dispersions to enhance release of poorly soluble drug. Solid dispersion using spray drying has also been used widely. Spray chilling or spray congealing is another form of solid dispersions used to enhance solubility [7, 8].

Chlordiazepoxide, a member of the 1, 4-benzodiazepine group, showing poor aqueous solubility and dissolution rate in water, was selected as model drug. The drug is a classical example of a solubility problem wherein it exhibits a 4000-fold difference in solubility going from pH 3 to 6 [9]. A study showed that in a group of 100 normal people over the age of 60, over 50% had hypochloridia (this simply means that they did not make enough hydrochloric acid). Patients with hypochloridia or achloridia usually have higher stomach pH which causes a reduction in the solubility of drug; hence a significant reduction in the dissolution rate of Chlordiazepoxide samples was observed. Therefore, the present investigation was focused to improve solubility and dissolution rate of Chlordiazepoxide by spray drying techniques using polymer i.e. Chitosan. Microspheres of Chlordiazepoxide were prepared by spray drying techniques using different drug: polymer ratio to improve solubility and dissolution rate of drug.

MATERIALS AND METHOD

Chlordiazepoxide and chitosan were procured from Rohm Pharma and IPCA lab, Mumbai, (India) respectively. 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 were used for the formulation of microspheres described in Table 1. The polymer solution was prepared by using 1% glacial acetic acid and water as solvent mixture, Chlordiazepoxide was added to the polymer solution and the resulting mixture was spray-dried, feed pump speed was 20 %.

Evaluation of microspheres:

Determination of drug loading:

The drug loading was determined by UV-Visible spectrophotometer. The microspheres were stirred with 100 ml of phasphate buffer for 2 h. The drug concentration was determined at 246 nm after suitable dilution. The readings were taken in triplicate.

Solubility studies:

The solubility of Chlordiazepoxide microspheres in water and pH 7.4 phosphate buffer was determined by

taking excess quantity of microspheres in 50 ml of 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 246 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 Philips X' Pert MPD Diffractometer, with Cu as anode material and graphite mono-chromator, operated at a voltage of 40 mA, 45 kV.

Scanning electron microscopy (SEM):

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:

Dissolution profile of Chlordiazepoxide sample and spray dried microspheres were determined by using USP dissolution apparatus XXIV-Type II (Electro Lab, Mumbai). Phosphate buffer 900 ml (pH 7.4) was used as dissolution medium. The amount of dissolved drug was determined by using UV spectrophotometric method (UV 1601 A Shimadzu, Japan) at 246 nm.

RESULTS AND DISCUSSION

During spray drying, if the drying temperature exceeds the transition temperature (at which a solid glass is transformed to a liquid like rubber) of polymer, the powder becomes soft or sticky while still warm. This causes sticking of the powder to the side walls of drying chamber. The transition temperature of chitosan is more than 100°C; therefore, water and 1% glacial acetic acid were used as solvent for chitosan microspheres. The drug loading and % yield of Chlordiazepoxide microspheres were determined and result showed in Table 1. In the solubility studies of the prepared microspheres with chitosan, formulation F-4; showed highest solubility of drug in both water (0.082mg/ml) and in buffer pH 7.4 (0.125 mg/ml) in comparison with pure drug; as the concentration of chitosan increased in the formulation, the solubility gradually increased up to a certain concentration followed by decrease in the solubility, showed in Table 1. The DSC thermogram indicates formation of uniform crystal during the spray drying process. DSC study of chitosan did not affect the DSC spectrum of Chlordiazepoxide, thus there was no change in physical properties of Chlordiazepoxide. The FTIR spectrum of pure drug compared with the spectrum of drug-polymer microspheres and showed in Fig 1. The Chlordiazepoxide exhibited its characteristic peaks at 1385 cm^{-1} (N-H stretching vibration), 1440 cm^{-1} (CH_3 and Ar-c=c stretching), 1355 cm^{-1} (sym. $-CH_3$) 770 and 740 or 740 cm^{-1} (substituted phenyl). The results of IR spectroscopy reveal that there was no chemical interaction between drug and the polymer. All the samples showed similar peak positions (2θ) in X-ray diffraction, formation of different polymorphs of Chlordiazepoxide was ruled out**.**

The SEM micrographs of pure Chlordiazepoxide and chitosan microspheres of Chlordiazepoxide are showed in Fig. 2. Size of pure drug was found to be 6-16 µm. The microspheres prepared by spray drying

were spherical in shape with small diameter in the range of 3–8 µm. The SEM images confirmed the uniformity and fine nature of the microspheres which contributed for the rapid drug release from the microspheres. The dissolution profiles of Chlordiazepoxide microspheres exhibited improved dissolution behavior than pure sample (Fg. 3). The formulation F4 showed better dissolution profile as compared to the other formulations made by changing drug: polymer ratio (Table 2).

Table. 1
Formulations of Chlordiazepoxide microspheres and their evaluations

Formulation	Drug: polymer ratio	% Yield	%Drug loading	Solubility in Water (mg/ml)	Solubility in buffer (pH 7.4) (mg/ml)
F1	1: 0.5	42.46	46.02±0.03	0.058 ± 0.005	0.076± 0.02
F2	1: 1	57.28	55.24±0.22	0.073± 0.003	0.087± 0.013
F3	1: 1.5	41.58	58.45±0.24	0.074± 0.010	0.105± 0.005
F4	1: 2	49.35	57.88±0.53	0.082± 0.006	0.125± 0.003
F5	1: 2.5	58.07	62.25±0.29	0.061± 0.013	0.077± 0.021

Table. 2.
% drug dissolved of different formulations of Chlordiazepoxide microspheres.

Time (min)	Drug Dissolved (%)				
	F1	F2	F3	F4	F5
0	0	0	0	0	0
5	15	53	90	100	50
10	15	61	91	98	55
15	17	63	93	100	57
20	30	65	93	100	59
30	35	65	93	100	60
45	37	65	93	100	60
60	38	65	93	100	60
100	40	65	93	100	60

CONCLUSION

Microspheres of Chlordiazepoxide with varying drug: polymer ratios were prepared by spray drying technique. Spray dried microspheres exhibited decreased crystallinity. DSC and XRD studies showed that there is no change in the crystal structure of Chlordiazepoxide during the spray drying process. The prepared microspheres showed good solubility and high % release compared to the pure sample of Chlordiazepoxide. Hence spray drying technique was found to be good method to improve solubility and dissolution of poorly water soluble drug using polymers i.e. chitosan. Hence these prepared microspheres can be used for the formulation purpose for Chlordiazepoxide.

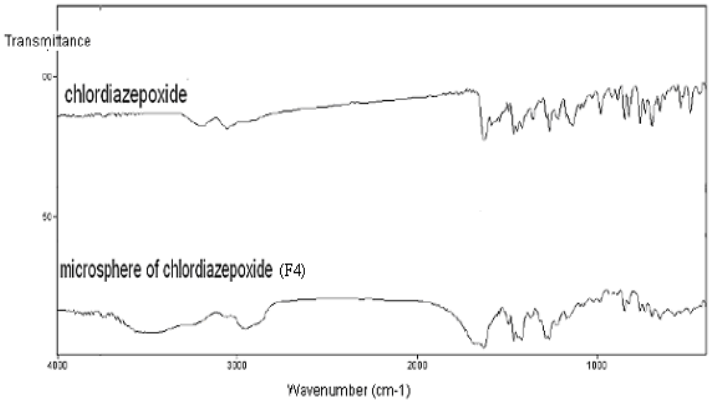


Fig. 1 FTIR spectra of drug and drug–polymer microsphere (F4)

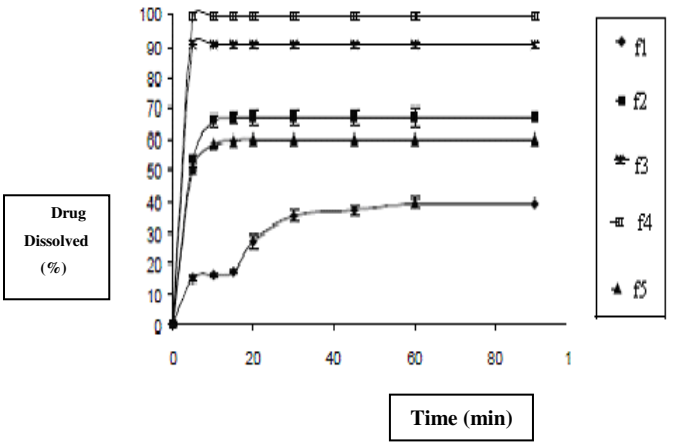


Fig. 3 Dissolution profile of spray dried microsphere of Chlordiazepoxide.

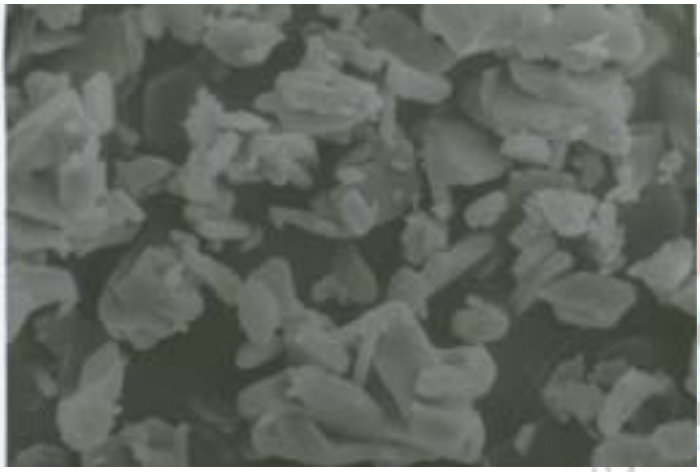
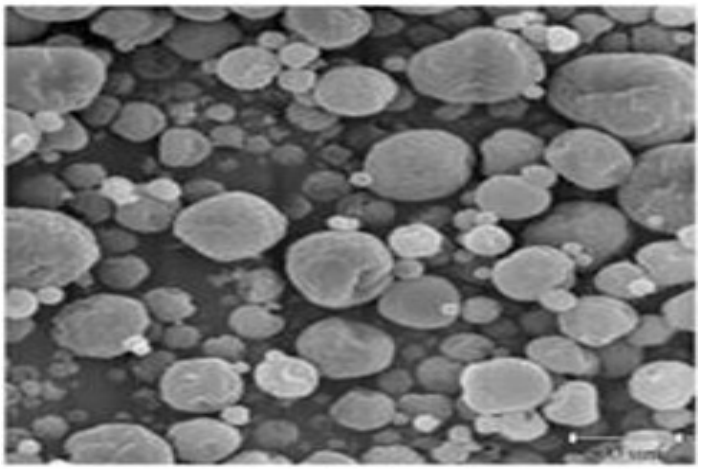


Fig. 2. SEM of Chlordiazepoxide



SEM of microspheres of Chlordiazepoxide

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