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FORMULATION AND EVALUATION OF PRAZOSIN HYDROCHLORIDE BY USING NATURAL POLYMERS LIKE GELATIN AND CHITOSAN

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ABSTRACT
The aim of this study was to formulate and evaluate microspheres as controlled release preparations of a highly water-insoluble drug, Prazosin HCL, using natural polymers, Chitoson and Gelatin materials. It is recently developed anti hypertensive drug used effectively in therapeutic practice. However, the Prazosin HCL has short half life and hence requires frequent administration. Therefore the possible way by which this can be overcome is formulating a controlled release formulation (CSR).

KEYWORDS: Prazosin HCL, CSR.

INTRODUCTION
The efficiency of any drug therapy can be described by achieving desired concentration of the drug in blood or tissue, which is therapeutically effective and non toxic for a prolonged period. This goal can be achieved on the basis of proper design of the dosage regimen. Microspheres have potential to deliver drug in a controlled fashion.

Prazosin Hydrochloride is indicated in the treatment of mild to moderate hypertension. Prazosin belongs to a family of selective antagonists of α1-adrenergic receptors.[1] It was the first α1-blocker introduced for the treatment of hypertension, acting in the expansion of the smooth muscle of small blood vessels and thereby lowering blood pressure.[2] Prazosin action involves vasodilation by the selective blocking of α1-adrenergic receptors located in the walls of blood vessels, direct inhibition of phosphodiesterase, as well as increasing cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) amounts. Prazosin hydrochloride also reduces cardiac preload and thus leads to a small increase in cardiac output and heart rate. It is also believed that prazosin hydrochloride works within the central nervous system, where it inhibits the sympathetic system and modulates the activity of baroreceptors.[2] The objective of this study is to develop a simple uncomplicated and easy to manufacture floating microspheres that is capable of delivering Prazosin Hydrochloride at a prolong release rate of delivery.

It may therefore be more desirable to deliver this drug in a sustained release dosage form. The present study was focused on development of controlled release prazosin hydrochloride microspheres using emulsification method and w/o emulsification solvent evaporation method. Microspheres can be defined as solid, approximately spherical particles ranging in size from 1 to 1000 µm. They are made of polymeric, waxy or other protective materials, that is, biodegradable synthetic polymer and modified natural products. Such as starches, gums, proteins, fats and waxes 1. The development of new delivery systems for the controlled release of drugs is one of the most interesting fields of research in pharmaceutical sciences.

Microparticles can be used for the controlled release of drugs, vaccines, antibiotics, and hormones. For example, by taking advantage of the characteristics of microspheres, beyond the basic benefits, the microspheres could provide a larger surface area and possess an easier estimation of diffusion and mass transfer behavior also the encapsulated small molecules could diffuse out of the barrier with precise kinetics modeling and control-release of drugs to the body fluid 2-3. Among the polymer systems employed, chitosan, a natural cationic polymer, has many advantages for developing microparticles in drug release applications. Chitosan is a derivative of chitin, the second most abundant polymer in nature, which is a supporting material of crustaceans, insects, and fungal mycelia 4-5. Among the different species of crustaceans, shrimp and

crab shells have been widely used for the isolation of chitosan.[3]

The use of controlled release systems has certain advantages compared with conventional dosage forms, as they can minimize side effects, and prolong the efficacy of the drug. These release forms regulate the drug release rate and can reduce the frequency of administration of the drug, thus assuring better patient compliance. The potential of chitosan as a novel excipient which might yet receive extensive application in pharmaceutical products has been highlighted in several reports.[4] The present research work was carried out with the aim to try to reduce Prazosin hydrochloride dosing frequency, as it is an antihypertensive producing a resistance if given in high frequency. So, if we can reduce the dosage frequency it will be more beneficial to all patients and treat then up to older age.[5] At the same time a single dosing for a treatment would lead to patient compliance, and complete treatment with appropriate dosing.

MATERIALS AND METHODS

Method of preparation of microspheres

Prazosin HCL (Taj pharmaceuticals LTD, Gujarat), Chitosan (Ranbaxy laboratories limited), Gelatin (S d chemicals limited, Mumbai), all other solvents and reagents used were of analytical grade. There exist several methods to prepare microsphere that differ as per the characteristics of polymers used, nature of microspheres, and nature of manufacturing condition.[6]

METHODS

Preformulation Studies

Preformulation testing is the first step in the rationale development of dosage forms of a drug substance. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. The overall objective of preformulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage forms, which can be mass-produced. Identification of prazosin hcl.[8]

Identification of prazosin hcl was carried out by FTIR spectrophotometry.

pH determination pH of prazosin hcl was carried out by digital pH meter.

Melting point determination: Melting point of prazosin hcl was determined by open capillary method.

UV spectroscopy

The first step in preformulation is to establish a simple analytical method so that all future measurements can be quantitative. Most drugs absorb light in ultravioletwavelengths (190 390 nm), since they are generally aromatic or contain double bonds. 100 mg of prazosin hcl was accurately weighed on electronic balance and dissolved in 100 ml methanol. Methanol is UV-transparent and a good solvent for most polar and non polar drugs.[9] Since this is anhydrous, potential hydrolysis is prevented and can serve as a stock solution. 1 ml of this solution was diluted with 100 ml of stimulated gastric fluid pH 1.2 and phosphate buffer pH 7.4 in separate volumetric flask and scanned on a UV scanner between 190 to 390 nm. The maxima obtained in the graph were considered as max for the prazosin hcl at respective buffers [Hejazi R, 2003].

Standard calibration curve for prazosin hcl in water 100 mg of prazosin hcl was dissolved in small amount of water and volume was made up to 100 ml using the same. From the stock solution serial dilutions were done to obtain solutions in the conc. ranging from 10 to 100 µg/ml. The absorbance of the solution was measured at 269 nm using UV-visible spectrophotometer. A graph of conc. v/s absorbance was plotted.[10]

Similarly, standard calibration curve of prazosin hcl were prepared in stimulated gastric fluid pH 1.2 and phosphate buffer pH 7.4 by using above said method.[11]

Characterization

The prepared microspheres were characterized by Fourier Transformed Infrared Spectroscopic analysis, The FT-IR spectral measurements were taken at ambient temperature using a Shimadzu, Model 8033 (USA) using KBr pellet method by applying 6000 kg/cm2 pressure to study the polymer-drug interactions. The SEM analysis of the microspheres was carried out by using Jeol JSM 5300, Japan, to determine size, shape and surface morphology of the prepared microspheres.

Evaluation

Content uniformity / drug loading

The prepared microspheres were powdered and passed through sieve no (85/120). The powder retained on the sieve 120 was taken for content uniformity studies. A weight of powder containing 100 mg of the drug was taken in a 100ml standard volumetric flask. To this of 0.1 N NaOH solution was added and made upto the mark with 0.1 N NaOH solution and kept overnight. The final solution was filtered using what man filter paper. From this 10 ml was pipetted out into a 100 ml standard volumetric flask and made up to the volume with 0.1 N NaOH solution and estimated spectrophotometrically for drug content.

In vitro dissolution studies

Dissolution studies were carried out by using USPXXIII dissolution test apparatus by rotating basket method in stimulated gastric fluid pH 1.2 for 2 h and in phosphate buffer pH 7.4 for remaining 10 h. The dissolution media were maintained at a temperature of 37 ± 50 C. The speed of rotation of basket maintained was 50 rpm.

The samples were withdrawn at 30 min intervals.

Procedure: prazosin hcl microspheres were placed in

basket in each dissolution vessel to prevent floating. 5 ml of dissolution media was withdrawn at predetermined time intervals and fresh dissolution media was replaced. The withdrawn samples were analyzed and the amount of prazosin hcl released was determined by UV absorption spectroscopy at 269 nm.

RESULTS AND DISCUSSION

FT-IR analysis

Drug polymer interaction (FTIR) study75FTIR spectroscopy was performed on Fourier transform infrared spectrophotometer(IR Affinity-1, Shimadzu, Japan). The pellets of drug and potassium bromide wereprepared by compressing the powders at 20 psi for 10 min on KBr-press and the spectra were scanned in the wave number range of 4000- 600 cm-1. FTIR study was carried on prazosin hcl, physical mixture of prazosin hcl and polymer, prazosin hcl microspheres and blank microspheres.[12]

Surface morphology (SEM)

Scanning electron microscopy has been used to determine particle size distribution, surface topography, texture, and to examine the morphology of fractured or sectioned surface. SEM is probably the most commonly used method for characterizing drug delivery systems, owing in large to simplicity of sample preparation and ease of operation. SEM studies were carried out by using JEOL JSM T-330A scanning microscope (Japan). Dry prazosin hcl microspheres were placed on an electron microscope brass stub and coated with in an ion sputter.[13]

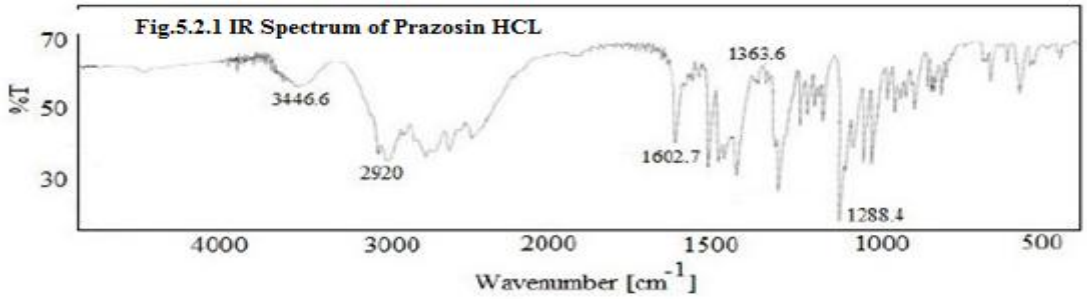
Content uniformity

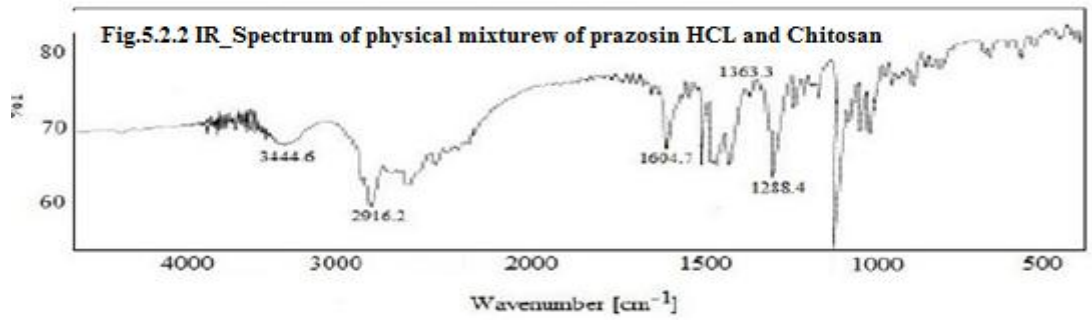
The test for content uniformity was carried out to ascertain whether the drug is uniformly distributed in the formulation. From the results it can be inferred that there is proper distribution of Indomethacin in the microspheres and the deviation is within acceptable limits.

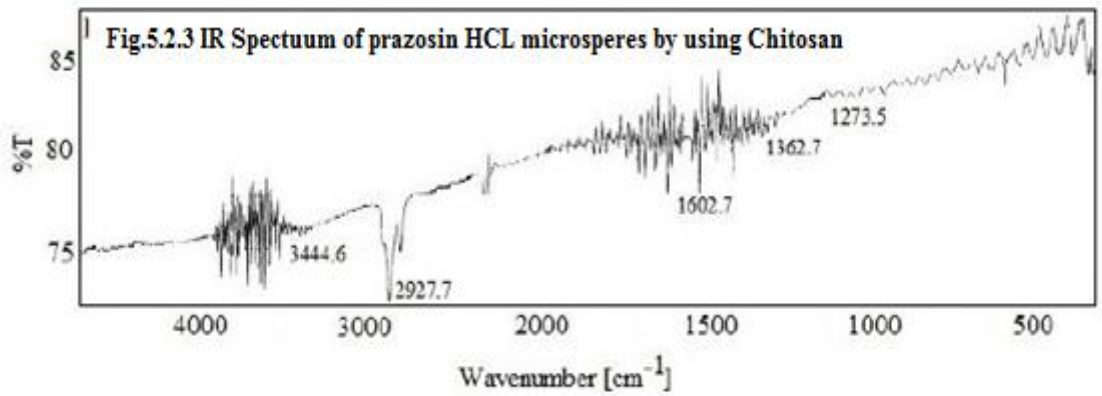
Table 1: IR Spectrum data.

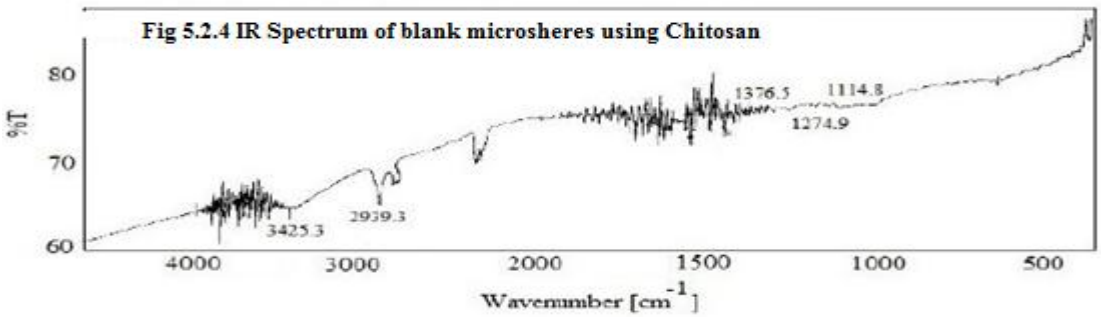
Sl.no	IR Spectrum	Peaks(cm-1)	Groups	Stretching/Deformation
1	Prazosin hcl	3446.6	N-H(2oamine)	Stretching
		2920.0	C-H(alkane)	Stretching
		1602.7	C=C(aromatic)	Stretching
		1363.6	C-N(3o amine)	Stretching
		1288.4	-O-(ether)	Stretching
2	Physical mixture of prazosin hcl and Chitosan	3446.5	N-H(2oamine)	Stretching
		2920.2	C-H(alkane)	Stretching
		1602.7	C=C(aromatic)	Stretching
		1363.3	C-N(3o amine)	Stretching
		1288.4	-O-(ether)	Stretching
3	prazosin hcl microspheres of Chitosan	3446.6	N-H(2oamine)	Stretching
		2927.7	C-H(alkane)	Stretching
		1602.7	C=C(aromatic)	Stretching
		1362.7	C-N(3o amine)	Stretching
		1273.5	-O-(ether)	Stretching
4	Blank microspheres of Chitosan	3425.3	O-H,N-H (hydrogen bonding)	Stretching
		2939.3	C-H(alkane)	Stretching
		1376.5	C-N(1o amine)	Stretching
		1274.9	C-O(alcohol)	Stretching
		1114.8	C-O-C(ether)	Stretching
5	Physical mixture of prazosin hcl and gelatine	3446.6	N-H(2oamine)	Stretching
		2920.0	C-H(alkane)	Stretching
		1602.7	C=C(aromatic)	Stretching
		1363.6	C-N(3o amine)	Stretching
		1288.4	-O-(ether)	Stretching
6	prazosin hcl microspheres of Gelatin	3446.6	N-H(2oamine)	Stretching
		2918.1	C-H(alkane)	Stretching
		1602.7	C=C(aromatic)	Stretching
		1361.7	C-N(3o amine)	Stretching
		1290.7	-O-(ether)	Stretching
7	Blank microspheres of Gelatin	3444.6	N-H(hydrogen bonding)	Stretching
		2916.2	C-H(alkane)	Stretching
		1687.2	C=O(ketone)	Stretching

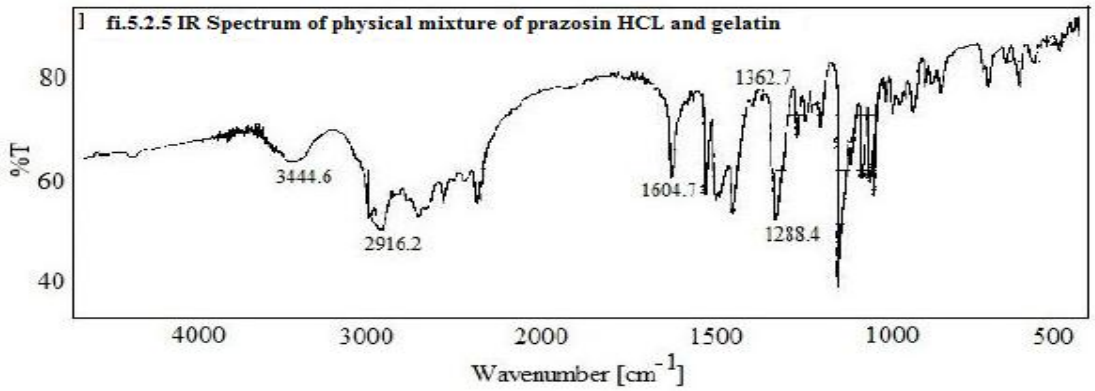
		1632.3	C=N(oxime)	Stretching
		1303.8	C-O(alcohol)	Stretching
		1164.9	C-O(alcohol)	Stretching
		1114.8	C-O-C(ether)	Stretching



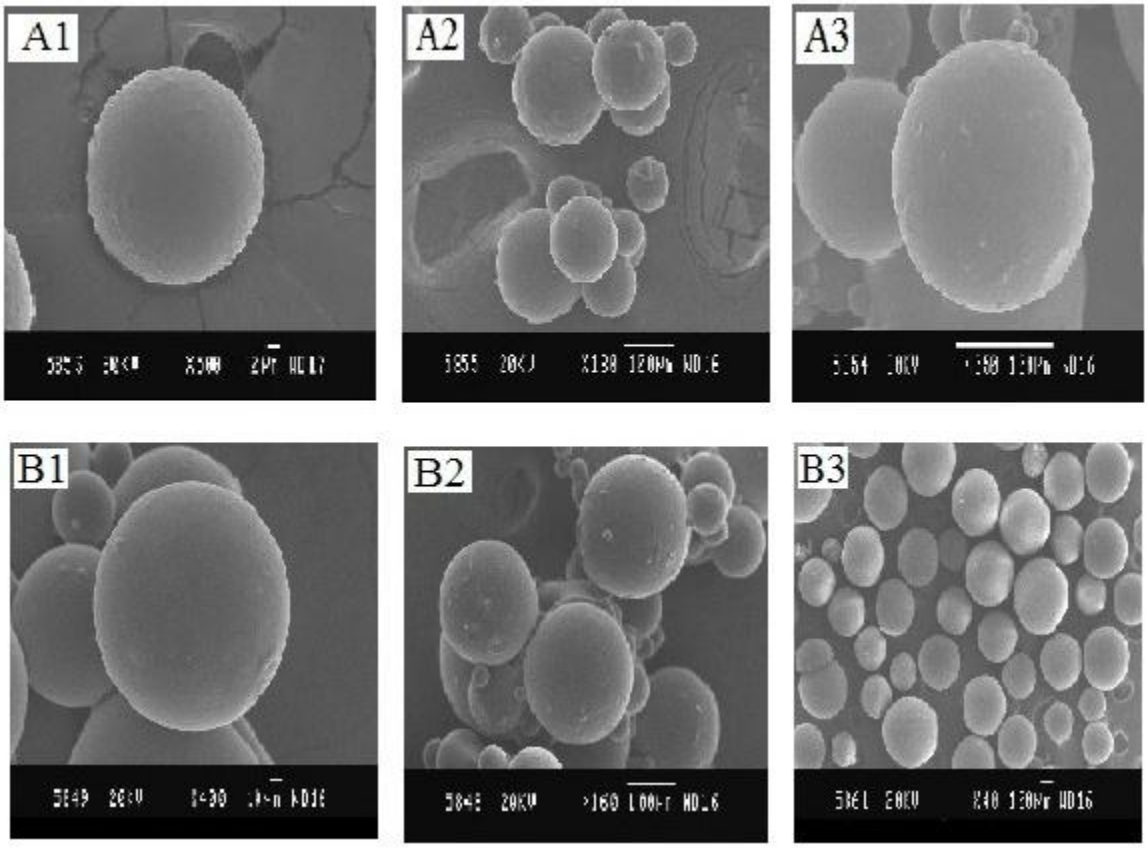








SURFACE MORPHPLOGY (SEM)



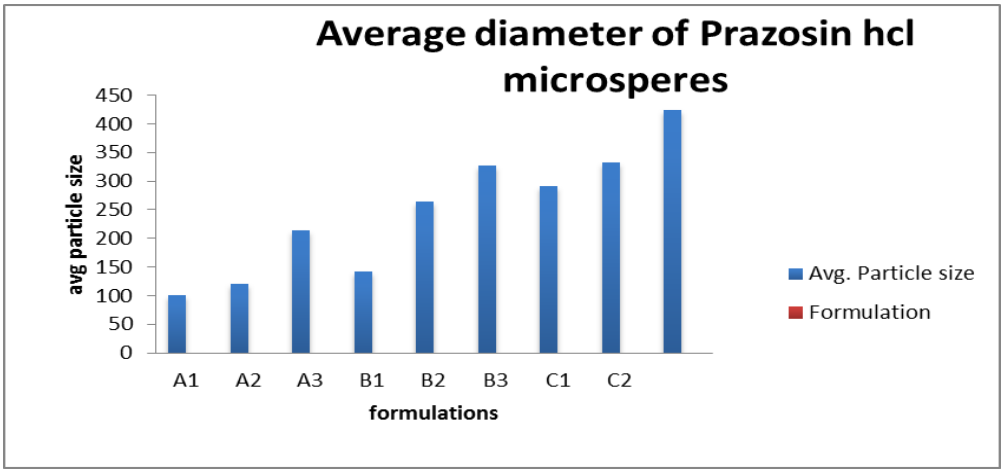
A1, A2 and A3 refer to prazosin hcl microspheres prepared by using Chitosan with drug: polymer ratio 1:1, 1:2 and 1:3.
B1, B2 and B3 refer to prazosin hcl microspheres prepared by using Gelatin with drug: polymer ratio 1:1, 1:2 and 1:3.

FREQUENCY DISTRIBUTION ANALYSIS

Determination of Average particle size.

Table 2: Average diameter of prazosin hcl microspheres.

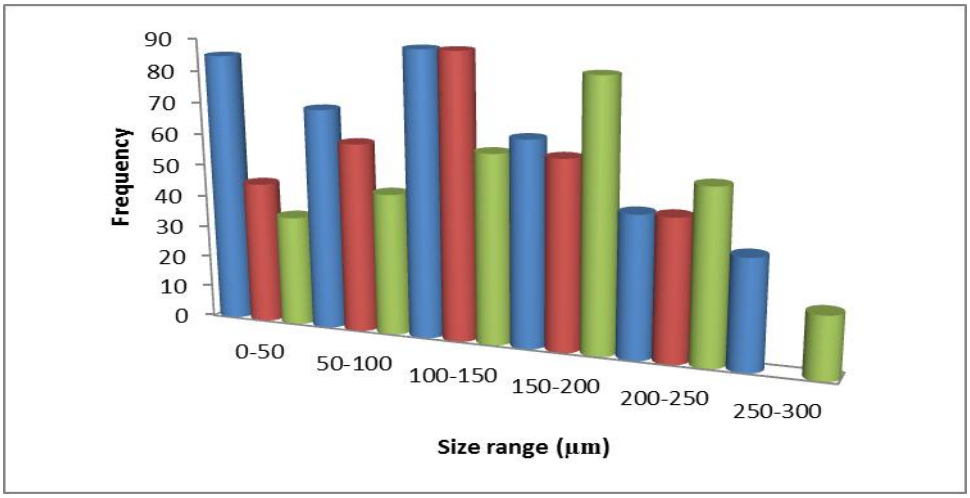
Sl.no	Formulation code	Average size(µm)±SEM
1	A1	100±6.73
2	A2	121±5.43
3	A3	214±7.62
4	B1	143±9.27
5	B2	265±8.63
6	B3	327±4.32
7	C1	291±8.26
8	C2	333±7.34
9	C3	424±8.17

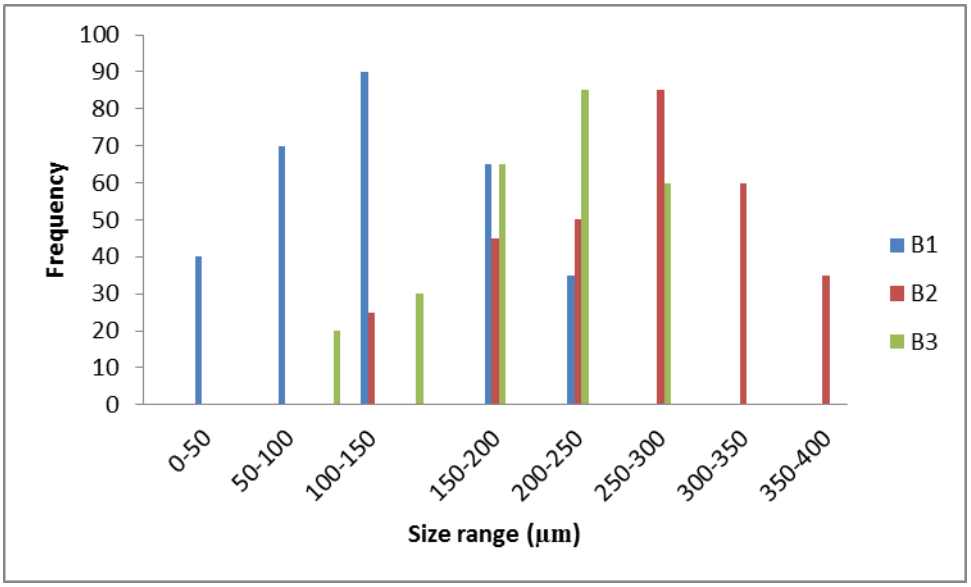


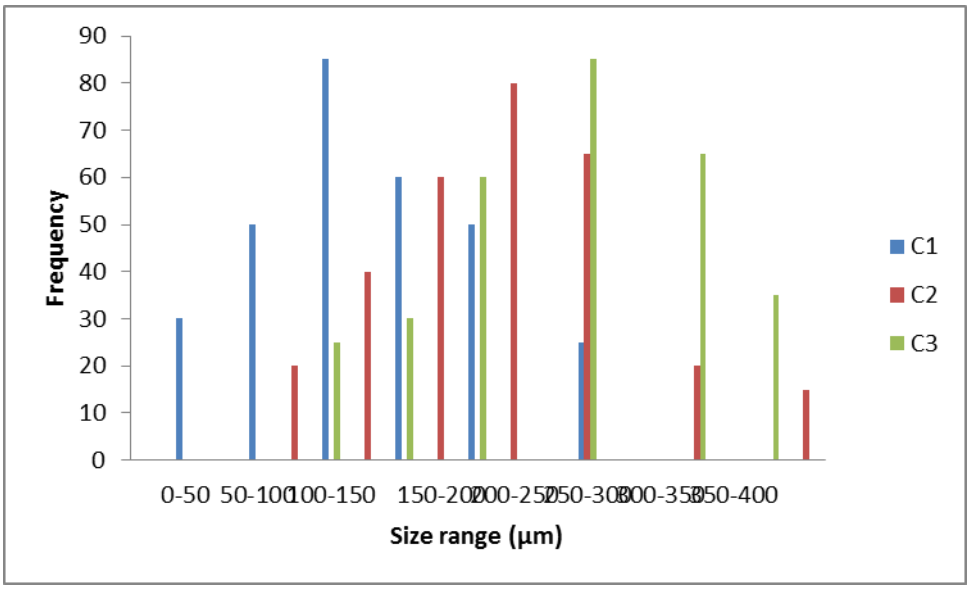
Frequency distribution analysis

Table 3: Frequency distribution data of Prazosin HCL microspheres.

Size range (um)	Number of particles								
	A1	A2	A3	B1	B2	B3	C1	C2	C3
0-50	60	45	35	85					
50-100	85	60	45	70					
100-150	60	90	60	90	25				
150-200	50	60	85	65	45	20	30	20	
200-250	45	45	55	35	50	30	50	40	
250-300			20		85	65	85	60	25
300-350					60	85	60	80	30
350-400					35	60	50	65	60
400-450						40	25	20	85
450-500								15	65
500-550									35







CONCLUSION

From the above experimental results it can be concluded that: Preformulation studies like pH, melting point, solubility and UV analysis of prazosin HCL were complied with BP standards. The FTIR Spectras revealed that, there was no interaction between polymers and prazosin HCL. All the polymers used were compatible with the prazosin HCL. Oral controlled release of prazosin HCL can be achieved by emulsification, suspension polymerization and emulsification solvent evaporation techniques by using polymers like Chitosan, Gelatin and Na CMC respectively. Surface smoothness of the prazosin HCL microspheres was increased by increasing the polymer concentration, which was confirmed by SEM.

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