

Formulation and Evaluation of Chitosan based Microparticulate Nasal Drug Delivery System of Rizatriptan benzoate

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Abstract: Microparticulate drug delivery systems provides numerous advantages like, increased surface area, modified release pattern, improved bioavailability etc. In the present work, attempt has been made to use chitosan, natural polymer for the preparation of microparticles by spray drying and evaluate them for size, shape, dissolution, mucoadhesion strength studies etc. For preparation of microparticles, model drug rizatriptan benzoate has been used.

It has been observed that, all drug loaded microparticles were spherical in nature with narrow size distribution. Spray drying induced drug amorphousation, which contributed for dissolution enhancement of drug. Also the loading of rizatriptan benzoate into chitosan microparticles led to an improvement of its dissolution/release rate. The rate of dissolution increases with increase in proportion of chitosan. In fact about 90–100% of drug release was achieved in less than 2 hr from the spray-dried microparticles. With the increase in proportion of chitosan in formulation (F1-F5) it has been observed that mucoadhesive strength of microparticles was increased due to decreasing mucocilliary clearance which increases residence time of drug in nasal cavity thus increasing absorption.

Present work was satisfactory attempt in employing technique of spray drying for developing microparticulate nasal drug delivery system for rizatriptan benzoate using chitosan as base.

Key words: Rizatriptan benzoate, Chitosan, Spray drying, Microparticles, Mucoadhesive, Mucocilliary clearance.

1. INTRODUCTION:

The objective of any drug delivery system is to provide therapeutic amount of drug to targeted site in body to achieve the desired therapeutic effect. In recent years, attention has been focused on the development of new drug delivery system rather than invention of new molecules. [1-2] Rizatriptan benzoate, is a selective 5-hydroxytryptamine 1B/1D (5-HT_{1B/1D}) receptor agonist commonly prescribing for treatment of migraine headache.[3-4] Theories on the etiology of headache suggest that symptoms are due to local cranial vasodilatation and/or to the release of vasoactive and pro-inflammatory peptides from

sensory nerve ending in an activated trigeminal system. Rizatriptan benzoate directly and selectively constricts intracranial, extracerebral blood vessels and inhibits the release of the sensory neuropeptides from perivascular nerves to prevent neurogenic vasodilation and extravasation in the dura matter. [5-6] Rizatriptan benzoate has been shown to relieve migraine within 2 hr in 67% to 77% of patients. [7-8] Oral bioavailability of rizatriptan benzoate is 40-45%. [9] Rizatriptan benzoate undergoes metabolism by monoamine oxidase A isoenzyme (MAO-A) to an inactive indole acetic acid metabolite. In addition, several other inactive metabolites are formed. An active metabolite, N-monodesmethyl-rizatriptan, with pharmacological

activity similar to that of the parent compound has been identified in small concentrations which may result in less bioavailability.

Hence in the present study an attempt is being made to maximize bioavailability of this drug by preparing chitosan based microparticles for nasal drug delivery system using spray drying.

Dry powder prepared from spray drying is a novel powder dosage form in which drug is molecularly dispersed into carrier or polymer as glassy solid solution. Typically spray-dried powders are amorphous in nature, due to their rapid solidification. [10-11]

Chitosan opens the tight junction of the mucosal barrier and facilitates the paracellular transport of hydrophilic macromolecules. [12-13-14] The strong mucoadhesive properties of chitosan point to its potential as a permeation enhancer for mucosal drug delivery. [15-16-17] Due to mucoadhesive properties of chitosan drug strongly adheres to mucosa and MCC is decreased thus increasing the residence time of drug in nasal cavity which results in increase in absorption. [18-19]

2. MATERIAL AND METHOD:

Rizatriptan benzoate was kindly supplied by. Chitosan was obtained as a gift sample from India Sea Foods, Chochin, Kerala. Other materials in the study were glacial acetic acid, methanol, sodium chloride, potassium chloride, calcium chloride. All chemicals used were of analytical grade.

2.1 EXPERIMENTAL DESIGN:

The batches for the experiment were designed such that every formulation will contain rizatriptan benzoate

and chitosan and the proportion of chitosan will be in increasing manner. Total 5 batches were taken in which the concentration of drug was kept constant throughout all batches. Thus the batches designed are shown in table no 1.

2.1.1 PREPARATION OF MICROPARTICLES BY SPRAY DRYING:

Chitosan was dissolved in 0.5% acetic acid solution at 1% (w/v) concentration. Rizatriptan benzoate was dissolved at 1% (w/v) concentration in 96% ethanol.[20] This solution was then mixed with chitosan solution and subjected to spray drying under optimized process parameters which are given in table no 2. Increasing concentrations of chitosan were used. Amount of drug and polymer taken are given in table no 1.

The prepared microparticles were then collected from drying chamber and cyclone separator carefully and then stored in dry atmosphere.

2.2 CHARACTERIZATION OF SPRAY DRIED MICROPARTICLES

2.2.1 SPRAY DRYING PROCESS YIELD:

The powder obtained from spray drying was mixed well and the product yield was calculated from the following formula:

$$\text{Product Yield (\%)} = \frac{\text{Product obtained from spray dryer}}{\text{Total dissolved solids}} \times 100$$

Here in this equation total dissolved solids (TDS) include the amount of drug and polymer added in the formulation. [21] Percent process yield of various batches is given in table no 3.

Table 1: Batches for experimental design and amount of ingredients taken

Sr. No.	Batch code	Drug: chitosan ratio	Amount of drug and polymer to be taken (mg)	
			Drug	Chitosan
1	F1	1:4	280	1120
2	F2	1:5	233	1166
3	F3	1:6	200	1200
4	F4	1:7	175	1225
5	F5	1:8	155	1244

Table 2: Optimized values of spray drying parameters

Sr. No.	Parameter	Optimized values for processing of dispersion containing drug and polymer
1	Input temperature	135°C
2	Output Temperature	80°C
3	Aspirator speed	75% or 350 mmWc (400 mmWc Max.)
4	Feed rate	6% or 45 mL/Hr (750 mL/Hr Max)
5	Compressed air pressure	3.5 barr

Table 3: Percent process yield of various batches

Sr. No.	Batch code	Percent Process Yield*
1	F1	50.71± 0.98
2	F2	48.57± 1.23
3	F3	51.11± 0.78
4	F4	50.00± 1.02
5	F5	56.42± 0.95

* Each value is average of three separate determinations ±SD

2.2.2 DRUG CONTENT DETERMINATION:

Samples containing exactly (10mg) of drug loaded microparticles were transferred to a 200ml volumetric flask. A total volume of 200ml of simulated nasal electrolyte solution (SNES) was added and dispersion obtained was sonicated for 1 min to dissolve rizatriptan benzoate. [22] Samples were filtered (PTFE 0.45µm) and concentration of rizatriptan benzoate in (SNES) was determined using a UV spectrophotometer at the wavelength of 282 nm. Theoretical and practical drug content and % drug recovery of the spray dried microparticles for various batches are given in table 4.

2.2.3 MOISTURE CONTENT DETERMINATION:

To determine the moisture present in the spray dried microparticles exactly 100 mg of powder was weighed and was dried in the hot air oven at 60 °C till constant weight. Percentage moisture content was then calculated by using equation:

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

Percentage moisture content in various batches of the spray dried microparticles determined by hot air oven is given in table no.5.

Table 4: Theoretical and practical drug content and % drug recovery of the spray dried microparticles for various batches

Sr. No.	Batch code	Theoretical Drug content(mg/10mg)	Practical Drug content(mg/10mg)*	% Recovery of drug
1	F1	2.00	1.96± 0.012	98.46
2	F2	1.66	1.63± 0.009	98.10
3	F3	1.42	1.41± 0.021	99.27
4	F4	1.17	1.13± 0.017	96.57
5	F5	1.03	1.01± 0.018	98.01

* Each value is average of three separate determinations ±SD

Table 5: Percentage moisture content in various batches of the spray dried microparticles determined by hot air oven

Batch code	% Moisture content*
F1	2.00±0.0324
F2	1.71±0.0905
F3	2.30±0.0056
F4	1.30±0.0245
F5	1.50±0.0133

* Each value is average of three separate determinations ±SD

2.2.4 SIZE, SHAPE, SURFACE CHARACTERIZATION OF MICRO PARTICLES:

Size, shape, and surface morphology of the rizatriptan benzoate, chitosan, and spray dried microparticles were determined by using scanning electron microscope.

2.2.5 DRUG-EXCIEPIENTS COMPATIBILITY STUDIES

2.2.5.1 INFRARED SPECTROSCOPY:

Fourier transform- infrared (FT-IR) spectra of drug, microparticles, chitosan were obtained on Jasco-4100 FTIR. The spectra were scanned over the wave number range from 4000 – 400 cm^{-1} . FTIR spectra of pure drug, chitosan, formulation (F1-F5) is given in fig. 3 and fig. 4.

2.2.5.2 DIFFERENTIAL SCANNING CALORIMETRY:

Thermograms of rizatriptan benzoate, chitosan, microparticles were obtained using differential scanning calorimetry instrument (TA Instruments SDT-2960, USA) equipped with an intracooler. Indium standard was used to calibrate the DSC temperature and enthalpy scale. The samples of dry spray dried microparticles were hermetically kept in the aluminum pan and heated at constant rate 10°C/min, over a temperature range of 10°C to 250°C. Inert atmosphere was maintained by purging nitrogen at the flow rate of 100 ml/min. DSC thermogram of pure drug, chitosan, formulation F2 and F3 is given in fig.5.

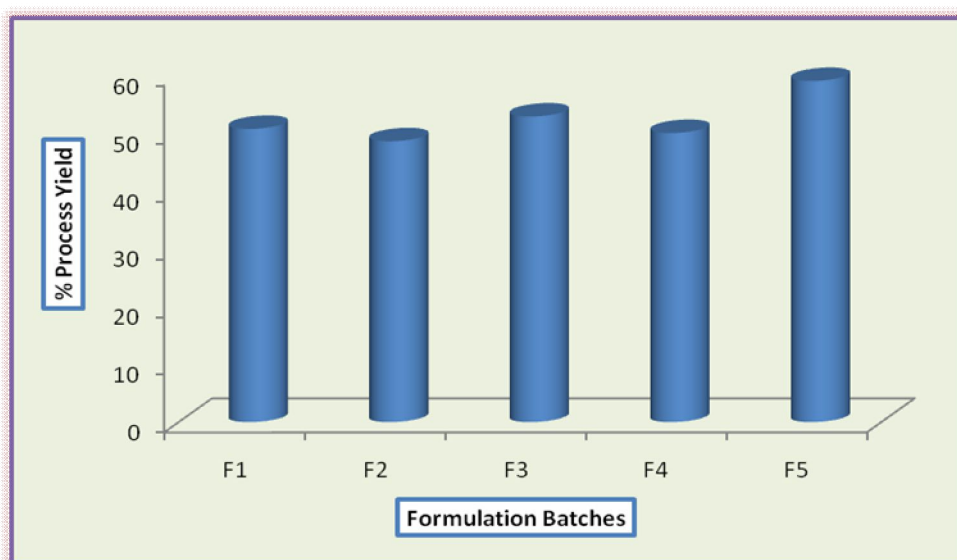


Fig. 1: Spray drying process yield for various batches

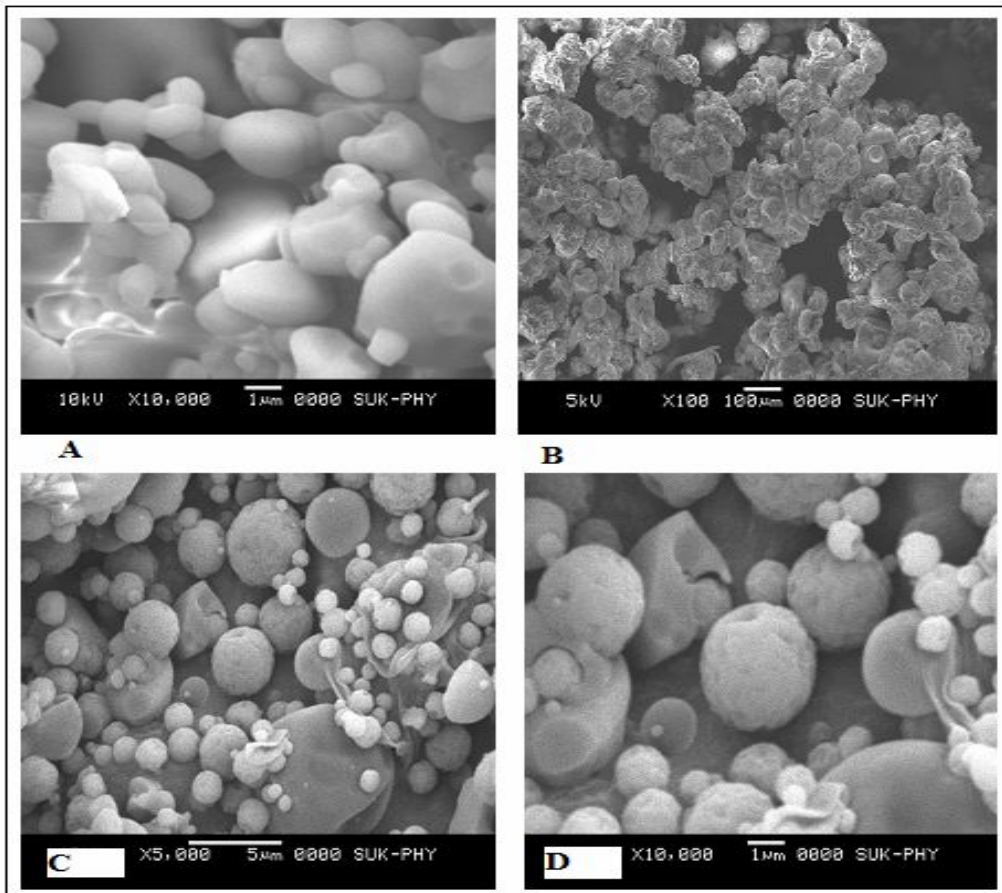


Fig. 2 : SEM image of A) rizatriptan benzoate B) chitosan C&D) formulation F2

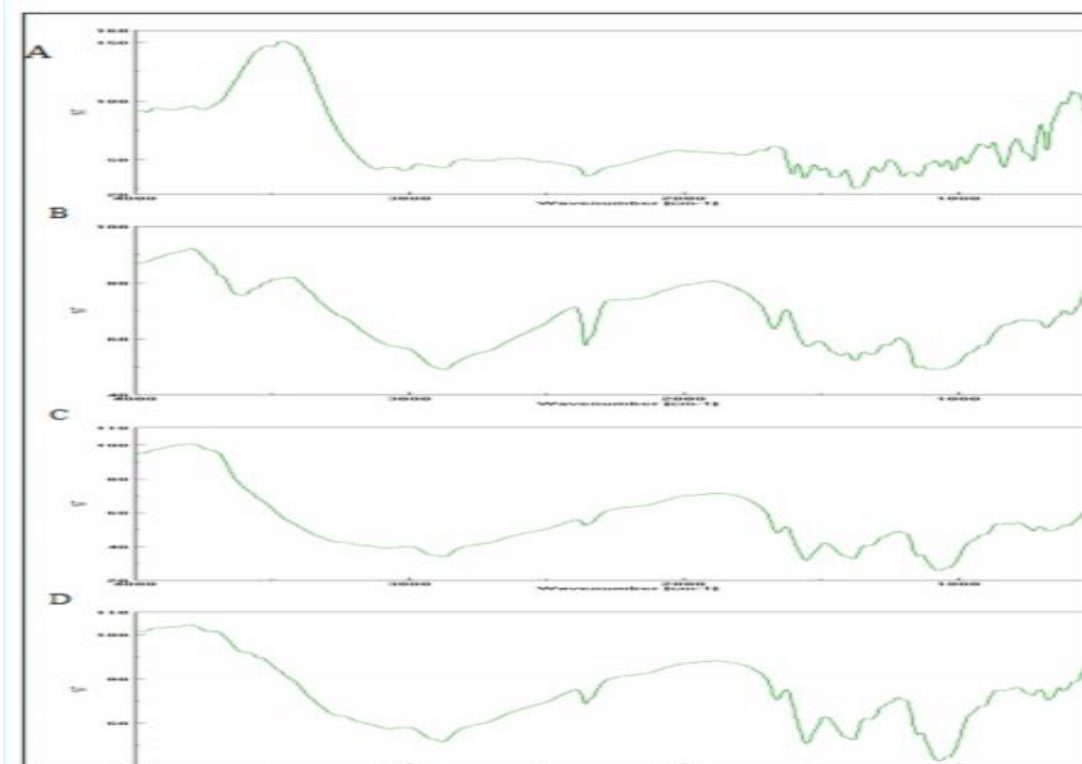


Fig. 3: FTIR spectra of A) pure drug B) chitosan C) formulation F1 D) formulation F2

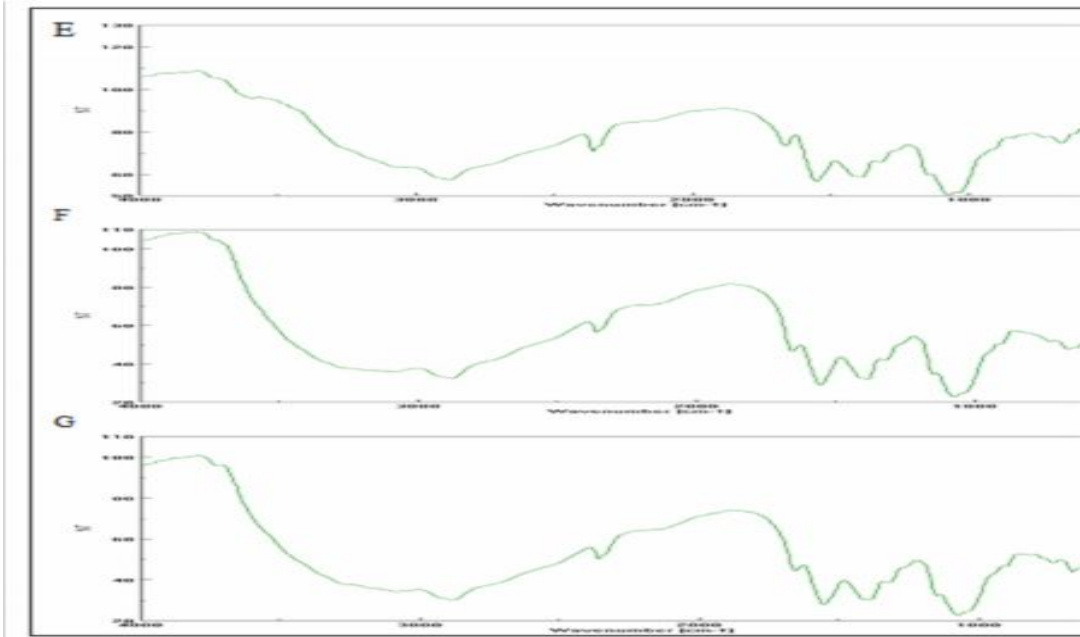


Fig. 4: FTIR spectra of E) formulation F3 F) formulation F4 G) formulation F5

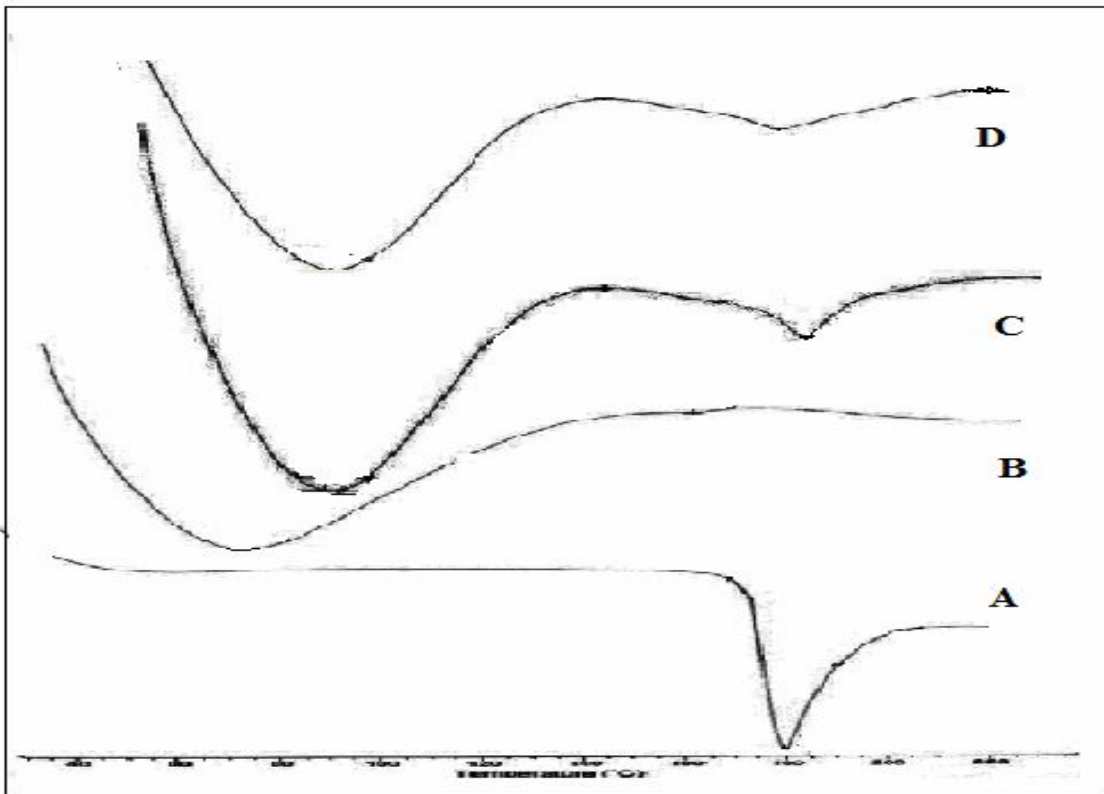


Fig.5: DSC thermogram of A) pure drug B) chitosan C) formulation F2 & D) formulation F3

2.2.6 POWDER X-RAY DIFFRACTION STUDIES:

To obtain the changes in the crystallinity of the microparticles prepared, the PXRD study was carried out by using X ray diffractometer (Philips PW-3710, Holland). For this the samples of pure drug, chitosan, prepared batches, were irradiated with monochromatised $\text{CuK}\alpha$ radiation and analyzed between from 5° to 60° (2θ). Powder X ray diffractograms of pure drug, chitosan, formulation (F1-F5) is given in fig.6 and fig.7.

2.2.7 IN VITRO RELEASE STUDIES:

In vitro drug release studies were performed with a USP (type 2) dissolution apparatus. Samples of

microparticles containing 10 mg of rizatriptan benzoate were tested in simulated nasal electrolyte solution. The rotational speed was set at 30 rpm and temperature for the dissolution medium was set at 37°C . Samples (5ml) were withdrawn at predetermined time points (3, 6, 10, 15, 25, 35, 50, 70, 90, 120, 180 min) and for each withdrawal the corresponding volume was replaced with fresh SNES of the same temperature. Samples were filtered (PTFE $0.45\mu\text{m}$) and assayed spectrophotometrically for rizatriptan benzoate at 282 nm. [23] Dissolution profile of formulation batches F1-F5 and of pure drug (F0) in simulated nasal electrolyte solution (SNES) is given in fig. 8.

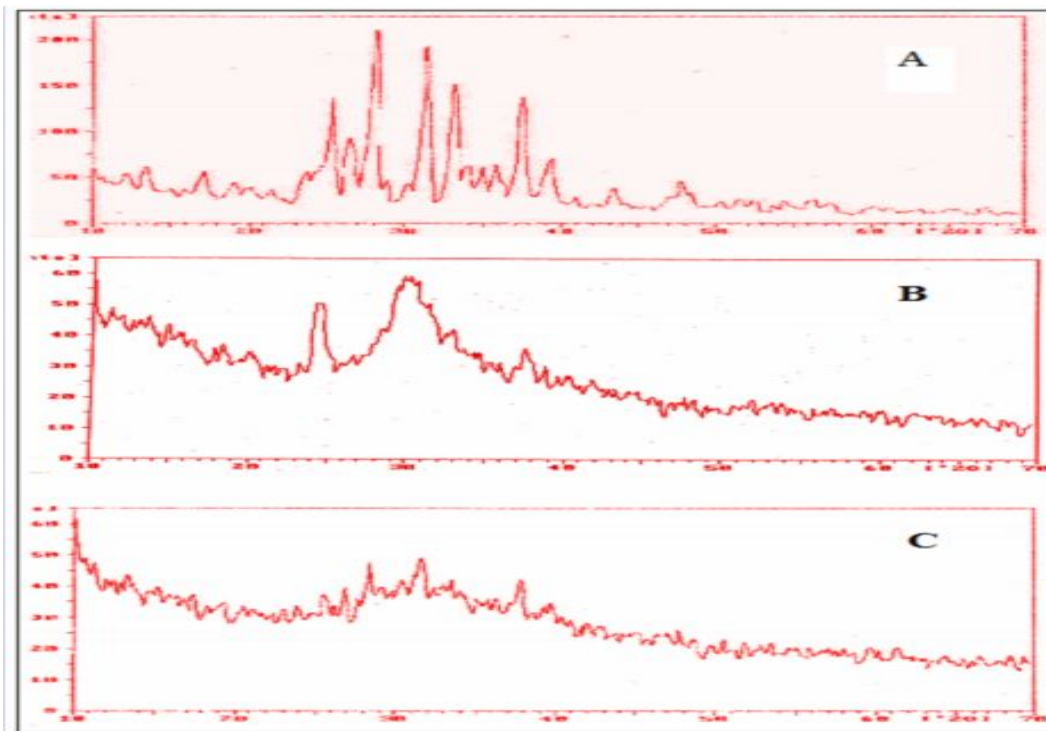


Fig 6: Powder X Ray Diffractograms of A) pure drug, B) chitosan, C) formulation F1

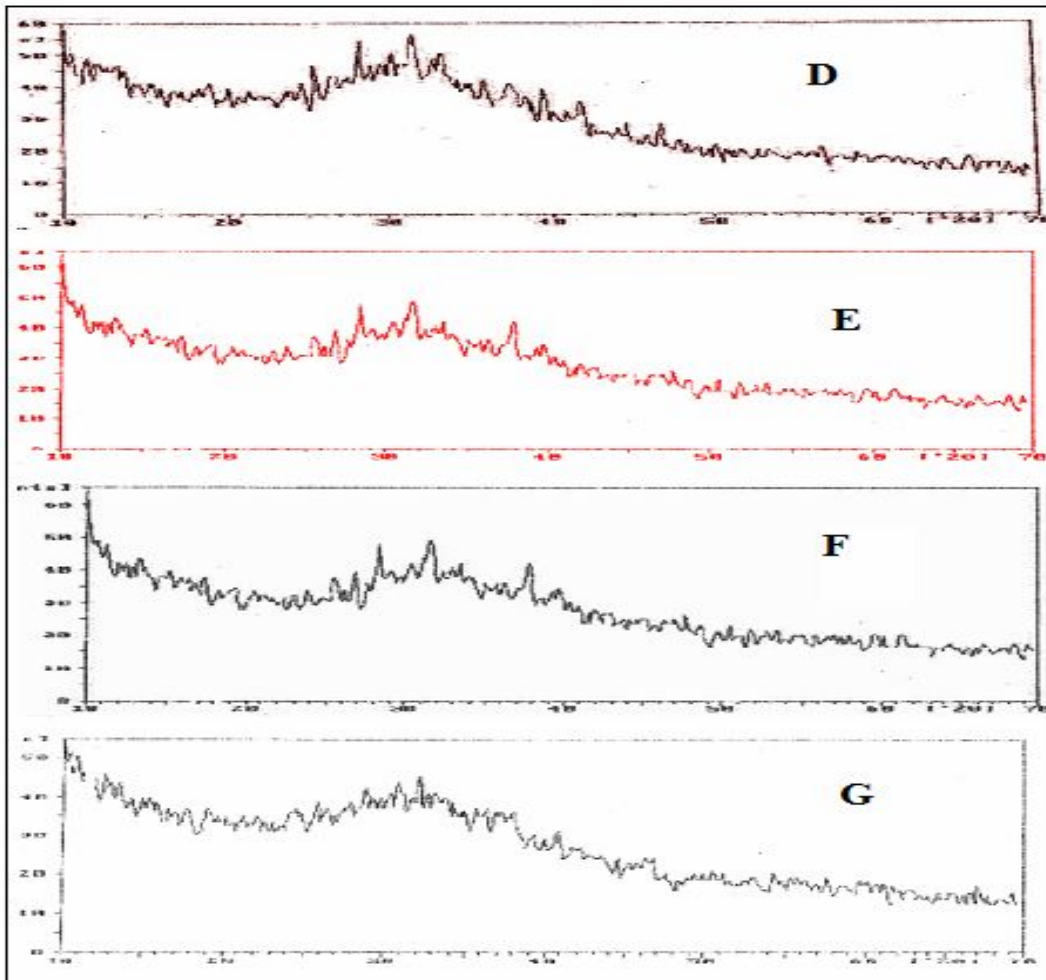


Fig 7: Powder X ray diffractograms of D) formulation F2, E) formulation F3, F) formulation F4 and G) formulation F5

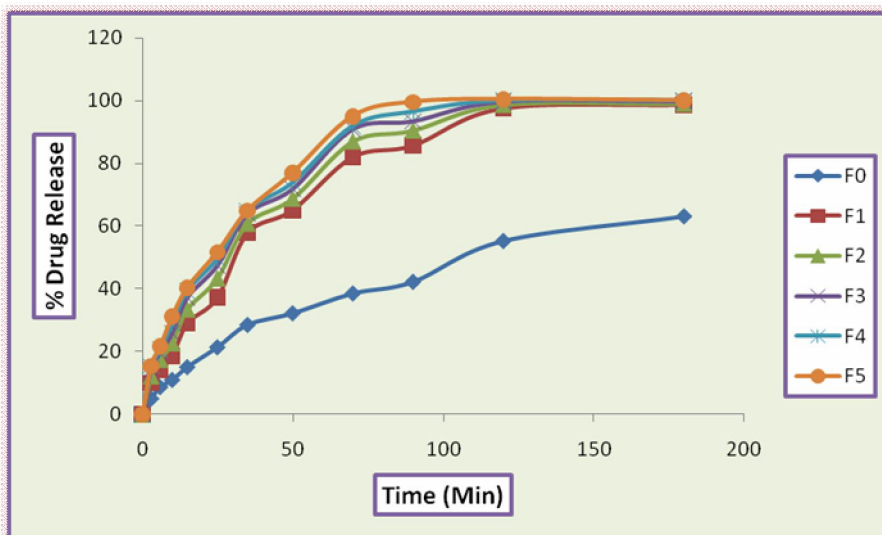


Fig. 8: Dissolution profile of formulation batches F1-F5 and of pure drug (F0) in Simulated nasal electrolyte solution (SNES)

2.2.8 EX-VIVO MUCOADHESION:

The ex-vivo mucoadhesion of microparticles was carried out by modifying the method described by Ranga Rao and Buri using sheep nasal mucosa. The dispersion (0.2 ml) of microparticles in water was placed on sheep nasal mucosa after fixing to the polyethylene support. The mucosa was then placed in the dessicator to maintain at >80% relative humidity and room temperature for 30 min to allow the polymer to hydrate and interact with the glycoprotein and also to prevent drying of the mucus. [24] The mucosa was then observed under microscope and the number of particles attached to the particular area was counted. After 30 min the polyethylene support was introduced into a plastic tube cut in circular manner and held in an inclined position at an angle of 45°. Mucosa was washed for 5 min with phosphate buffer saline pH 7.4 at the rate of 22 ml/min using a peristaltic pump tube carrying solution was placed 2-3 mm above the tissue so that the liquid flowed evenly over the mucosa. Tissue was again observed under microscope to see the number of microparticles remaining in the same field. The adhesion number was found by the following equation: $N_a = N/N_0 \times 100$, where N_a is adhesion number, N_0 is total number of particles in a particular area, and N is number of particles attached to the mucosa after washing.

Percent mucoadhesion of various batches (F1-F5) is given in fig. 9.

3 .RESULTS AND DISCUSSION

3.1 PROCESS YIELD:

In the spray drying process it is difficult to get more yield and up till now the reported process yield was in the range of 30-50%, with our optimization process we came with considerable higher amount of amount of yield. From the table no 3 and fig no 1 it can be seen that the process yield obtained is within the range of 48-55%.

3.2 DRUG CONTENT DETERMINATION:

Drug content of batches containing chitosan and rizatriptan benzoate was determined by UV spectroscopic method. The amount of drug in spray dried batches was found proportionately near to that of incorporated drug, and the maximum wastage was that of polymer added and not of drug. This might also be due to excess loss of polymer while other processes. Theoretical and practical drug content and percentage drug recovery of various batches of spray dried microparticles are as shown in table no 4.

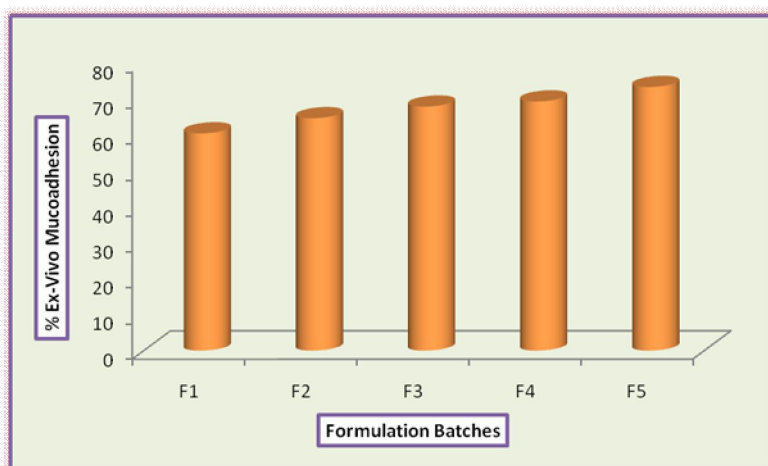


Fig. 9: Percent mucoadhesion of various batches (F1-F5)

Table 6: Percent mucoadhesion of various batches (F1-F5)

Sr. No	Batch Code	% Ex-vivo Mucoadhesion
1	F1	61.66
2	F2	64.70
3	F3	67.74
4	F4	68.51
5	F5	72.30

3.3 MOISTURE CONTENT DETERMINATION:

Moisture content of formulated batches was determined during storage, by using hot air oven and was found within the range of 1.3 to 2.3 %. The moisture content obtained for individual batches are given in table no 5.

3.4 PARTICLE MORPHOLOGY:

Size, shape, and surface morphology of the rizatriptan benzoate, chitosan, and spray dried microparticles were determined by using scanning electron microscope. SEM image of rizatriptan benzoate, chitosan and formulation F2 shown in fig no 2. Visual examination of the SEM pictures indicated that the microparticles of spray-dried chitosan (formulation F2) were spherical with varied surface roughness. Similarly, all the spray-dried rizatriptan benzoate – chitosan microparticles were spherical, irrespective of chitosan type or proportion. The spherical shape, formed as the droplet dries in the stream of hot air, is characteristic of amorphous spray-dried powders.

3.5 DRUG-EXCIEPIENTS COMPATIBILITY STUDIES

3.5.1 FTIR SPECTROSCOPY:

FTIR spectra of pure rizatriptan benzoate, chitosan and various formulations (F1- F5) were shown in figure 3 & figure 4. From the figure it was confirmed that there is no interaction between drug and polymer because the IR spectra of all formulations retains the principal drug peaks at 3432.13 cm^{-1} (NH stretch), 1608.65 cm^{-1} (C=C), 1503.23 cm^{-1} (C=N), 1445.13 cm^{-1} (CH₂ group), 1570.53 cm^{-1} (N-H blend), 1376.93 cm^{-1} (CH₃ group). The FTIR spectra of all formulations (F1- F5) did not show any new peak, indicating no new chemical bond was created due to any interaction.

3.5.2 DIFFERENTIAL SCANNING CALORIMETRY:

Thermal analysis rizatriptan benzoate, chitosan, microparticles was performed by differential scanning calorimetry. The representative thermograms of pure drug, chitosan, batch F2 and F3 are shown in fig no 5. Thermal analysis indicated that the DSC scan of the drug presented a sharp endothermic peak at 180°C corresponding to its melting transition temperature. The broad band of chitosan was observed at 72.50°C. The melting endotherm of rizatriptan benzoate is found retained in the thermograms of formulation F2 (1:5) as well as formulation F3 (1:6) shows no interaction, as such occurs between drug and excipients. The reduced intensity of the peak might be due to presence of drug in lesser quantity and polymer in higher quantity. The DCS thermogram does not show any new peak which confirms that there is no any new bond was created in the formulation.

3.6 POWDER X-RAY DIFFRACTOMETRY:

In the powder X-ray diffraction studies, the diffractograms of the representative batches were taken to find out the effect on the crystallinity of the excipients. The X-ray diffractograms of the pure drug, chitosan and formulation batches F1-F5 are shown in fig no 6 & fig no 7. The raw rizatriptan benzoate showed several characteristics peaks at 2θ angle 25.50° , 26.44° , 28.21° , 31.23° , 31.54° . These PXRD pattern shows that raw rizatriptan benzoate was crystalline in nature. Rizatriptan benzoate microparticles prepared by spray-dried method shows diffused halo pattern, demonstrating its amorphous nature which is most useful for enhancement of its bio-availability from nasal route of administration.

3.7 IN VITRO RELEASE STUDIES:

In vitro release studies were carried out and enumerated in fig no 8 which shows in vitro release profiles obtained from the drug-loaded microparticles compared to the dissolution profile of the drug alone. The rate of dissolution of rizatriptan benzoate powder was significantly slow (approximately less than 40% of the drug dissolved in 3 hr). The loading of rizatriptan benzoate into chitosan microparticles led to an improvement of its dissolution/release rate. The rate of dissolution increases with increase in concentration of chitosan. In fact about 90–100% of released drug was achieved in less than 2 hr from the spray-dried microparticles.

3.8 EX-VIVO MUCOADHESION:

The ex-vivo mucoadhesion indicates that microparticles had good mucoadhesive property and could adequately adhere on nasal mucosa. It was observed that increase in proportion of polymer, chitosan increased mucoadhesive strength of microparticles. This can be due to modification of the permeability of the nasal membrane by employment of absorption enhancers such as chitosan which can increase the absorption of drugs and the use of mucoadhesive systems such as bioadhesive liquid formulations, microspheres, powders and liquid gelling formulation that decrease mucocilliary clearance of the drug formulation and thereby increase the contact time between the drug and site of absorption. Percent ex-vivo mucoadhesion is given in table no 6 and fig no.9.

4. CONCLUSION

The technique of spray drying successfully developed chitosan based microparticles for nasal drug delivery. The microparticles obtained by spray drying had excellent surface morphology, better mucoadhesion.

The release of rizatriptan benzoate was significantly slow (approximately less than 40% of the drug dissolved in 3 hr). The loading of rizatriptan benzoate into chitosan microparticles led to an improvement of its dissolution/release rate. The rate of dissolution increases with increase in concentration of chitosan. In fact about 90–100% of released drug was achieved in

less than 2 hr from the spray-dried microparticles and signifying role of chitosan in design of microparticles. Thus it can be concluded that use of chitosan decreases mucocilliary clearance increases residence time of drug in nasal cavity thus increasing absorption and ultimately increased bioavailability is achieved.

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