ORIGINAL ARTICLE

# Formulation development and evaluation of orally disintegrating tablets of doxazosin mesylate

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Doxazosin mesylate has some of the ideal characteristics required for an orally disintegrating tablet. There were some challenges faced during this formulation development. The aims of the present research were to mask the bitter taste of Doxazosin mesylate and to formulate orally disintegrating tablets of taste masked drug. Taste masking was performed by coating Doxazosin Mesylate with suitable polymer Eudragit powdered E-100 using spray drying technique. The resultant microspheres were then evaluated for thermal analysis, yield, particle size, entrapment efficiency and *in vitro* taste masking. The tablets were formulated by mixing the taste masked microspheres with different types and concentration of super-disintegrants and granulated Mannitol was selected as diluent and compressed using direct compression method. The tablets prepared were evaluated for weight variation, thickness, hardness, friability, drug content, water content, *in vitro* disintegration time and *in vitro* drug release and compared with marketed IR tablet of Doxazosin mesylate.

***Key words:*** *Disintegration time, doxazosin mesylate, orally disintegrating tablet, spray drying, taste masking*

## INTRODUCTION

The oral route of drug administration is the most common and convenient for patient use.

Tablets and capsules have emerged as the most popular solid oral dosage form among the masses today. It includes conventional and modified release tablets as well as hard and soft gelatin capsules. Solid orals have wide acceptance worldwide as compared to other dosage forms. Around 50-60% of total dosage forms include solid orals alone. These figures speak itself for the popularity of solid oral dosage forms. The ease of administration and the belief that by oral administration drug is well absorbed are the prime reasons for such popularity.

However many patients, especially geriatrics have dysphagia or difficulty in swallowing tablets and hard gelatin capsules. In these cases orally disintegrating tablets have been found to be immensely useful. Thus most geriatric patients prefer orally disintegrating tablets. Water has an important role in the swallowing of oral dosage forms. Patient might find it difficult in case if there is no availability of water for oral administration. Especially in case of motion sickness when the patient is travelling or if there is any sudden episode of coughing during allergic conditions, Bronchitis, etc.

The main objective of mouth dissolving drug delivery system is to improve the patient compliance. There is rapid disintegration of these dosage forms as they come in contact with the saliva. Thus saliva is enough for the dosage form to disintegrate which obviates the use of water. Dysphagia is experienced by patients suffering from AIDS, Parkinson's disease and other neurological disorders including Cerebral Palsy. Geriatric patients find it utmost difficult to swallow oral solid dosage forms since they require even other dosage forms and medicines to maintain healthy life.

Benign Prostatic Hyperplasia (BPH) is a common cause of urinary outflow obstruction. BPH can present as reduced

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urinary flow rate, arising from either benign excessive growth of prostatic tissue or increased prostatic smooth muscle tone, both of which cause urethral pressure and obstruction. The prevalence of BPH increases with age, with >70% of men aged 61-70 years and 90% of men aged >80 years presenting with histological evidence of BPH. The therapeutic goal is to relieve the symptoms of BPH, improve patients' quality of life, decrease postvoid residual urine volume, and help to prevent the morbidity associated with untreated BPH through early detection and effective therapy. Thus BPH is associated with geriatric population. Geriatric population have the problem of Dysphagia i.e., difficulty in swallowing. This can be avoided by the formulation of an orally disintegrating tablet. Thus Doxazosin Mesylate is an ideal drug candidate for Orally disintegrating tablet formulation but Doxazosin Mesylate is very bitter in taste so to overcome the problem the formulation is designed in such a way that taste masking improves patient compliance at the same time coating of polymer for tastemasking does not interfere in drug release and disintegration.[1-3]

## MATERIALS AND METHODS

### Materials

Doxazosin mesylate was purchased from Aurobindo Pharma Pvt. Ltd. (Hyderabad, India). Dextrose was purchased from S.D. Fine chemicals, Eudragit® powdered E-100 (EPO) was kindly gifted by Degussa India Pvt. Ltd., Mannitol (Roquette frères, France), Kollidon CL-F (BASF India), Polyplasdone XL (ISP Sales, UK), Polacrilin Potassium (Ion Exchange India Ltd., Gujarat), Croscarmellose Sodium, (FMC Biopolymer, Ireland), Magnesium Stearate (Peter Greven, Malaysia), Talc (Luzenac Europe, France), Aspartame (NutraSweet company, USA), Peppermint Flavour (Symrise Pvt. Ltd., Chennai) were also gifted. Isopropyl Alcohol was purchased from Hufort Healthcare Pvt. Ltd., Mumbai. Potassium dihydrogen phosphate was purchased from Merck, India. Equipment used in this research were as follows: Spray Drier (Labultima LU 222), Analytical Weighing balance (BSA 224 S, Sartorius), Fluid Bed Processor (Bectochem), Cmb4 Double Sided Rotary Tablet Press (Cadmach), Hardness tester (Erweka), Friabilator (Electrolab), Dissolution apparatus (Electrolab), UV Spectrophotometer (V630, Shimadzu, Japan), FT-IR (8400S, Shimadzu), Digital microscope (DMWB-1, Motic), Differential Scanning Calorimeter (Perkin Elmer).

### Preparation of spray dried microspheres

Doxazosin mesylate taste masked microspheres were prepared by spray drying technique with drug: polymer ratios of 1:1, 1:2, 1:3, 1:4, 1:5. The polymer Eudragit EPO was dissolved in isopropyl alcohol and then drug was added to prepare a suspension. The prepared suspension was stirred using Remi stirrer at 500 RPM to maintain uniformity and sprayed through a nozzle (0.7 mm) using a spray drier (Labultima LU222). The spray drier was operated under following conditions.

Inlet temperature 85-90°C, outlet Temperature 60°C Vaccum 110 mmWC, Aspirator 2.2 kg/cm$^2$, and Feed pump operated at 75 ml/h.[4-6]

### Taste evaluation of microspheres

#### *Determination of taste recognition threshold of doxazosin mesylate*

The bitter taste threshold value of DOX was determined based on the bitter taste recognized by nine volunteers (two female, seven males) in the age group of 24-32 years. Aqueous solutions of DOX with different concentrations (2,6,11,16,20 µg/ml) were prepared. One milliliter of solution was placed on the center of the tongue of volunteer for 30s. The solution was spat out after 30s and the mouth was thoroughly rinsed with distilled water. A gap of 30 min was maintained in between tasting two different solutions. The same procedure was repeated for DOX solutions with concentrations (7,8,9,10 µg/ml). The threshold value was selected on the basis of lowest concentration that had a bitter taste.[7,8]

#### *In vitro taste masking evaluation*

The study was conducted in accordance to the method adopted from Shukla, *et al.* The required amount of spray dried microspheres equivalent to 8mg was placed in a 25 ml beaker. A volume of 10 ml of phosphate buffer solution pH 6.8 (United States Pharmacopoeia (USP)) was added and the mixture was allowed to stand for 60s. Phosphate buffer pH 6.8 was used to mimic the salivary fluid volume and pH. After the specified time, the suspension was filtered through 0.45 µ nylon membrane filter. The filtrate was analysed for DOX concentration at 245 nm by UV/Visible spectrophotometer (Shimadzu) and that was compared to bitter threshold value.[7-9]

#### *Particle size*

The analysis was performed by optical microscopy using Motic microscopy.

### Drug entrapment efficiency, loading and yield

The entrapment efficiency and drug loading in microspheres was estimated by dissolving 50 mg of microspheres in 0.01 N HCl. The samples were analyzed using UV/Visible spectrophotometer (Shimadzu UV 1800) at a wavelength 245 nm. Entrapment efficiency, drug loading and yield were calculated using the following equations:[7,8-10]

$$\text{Drug entrapment efficiency } (\%) = \frac{\text{Weight of drug in microspheres}}{\text{Weight of drug fed initially}} \times 100 \quad (1)$$

$$\text{Drug loading } (\%) = \frac{\text{Weight of drug in microspheres}}{\text{Weight of Microspheres}} \times 100 \quad (2)$$

$$\text{Yield } (\%) = \frac{\text{Weight of microspheres}}{\text{Weight of drug and Eudragit EPO}} \times 100 \quad (3)$$

### Thermal analysis

Differential scanning calorimetry (DSC) was used to evaluate the compatibility between Doxazosin mesylate and Eudragit EPO. The DSC experiments were then carried out by sealing accurately weighed samples (3-5 mg) in flat bottom aluminium pans and thermo gram were recorded at a constant rate of 10°C/min over a temperature range of 40-400°C performed on plain drug, Eudragit EPO and spray dried drug loaded microspheres.

### Infrared spectroscopy

Infrared spectroscopy was conducted using Fourier transform IR Spectrophotometer (FTIR-Shimadzu) and for DOX, polymer-Eudragit EPO, drug and polymer.

### Scanning electron microscopy

The photomicrographs were obtained using Scanning electron microscopy (JSM-6360 A, JEOL, Japan) in University of Pune. The microspheres were mounted on a double-faced adhesive tape and sputtered with platinum and the samples were scanned at 20 kV voltage. The micrographs were examined at a magnification ratio of ×1,000.

### Formulation development

*For batches F1 and F2*

The tablets were prepared by direct compression. The taste masked Doxazosin Mesylate i.e., spray dried microspheres containing drug and polymer at a ratio of 1:3 (32.5 mg equivalent to 8 mg of Doxazosin mesylate), Mannitol, dextrose, aspartame and peppermint flavor were accurately weighed. The ingredients were passed through 40 # and mixed geometrically as per the formula in Table 1. The obtained blend was lubricated with magnesium stearate before compression. The blend was compressed on a Tablet press machine (Cadmach Double rotary tablet press) using a flat 8 mm punch with beveled edge. The tablet weight was kept at 250 mg and hardness was maintained in the range of 30-35 N. The tablets were then packed and sealed in a HDPE bottle with a desiccant.

### Evaluation of tablets, physical properties of tablets

Twenty tablets were selected randomly to determine weight variation. The tablets were weighed individually using an electronic balance and compared with an average weight. The thickness of the tablet was evaluated using Vernier calliper (MITUTOYO). Hardness of the tablet was determined using the Erweka Hardness tester in the units of Newton. The mean hardness of 10 tablets was calculated and reported. Twenty six pre-weighed tablets were rotated at 25 RPM for 4 min in Friability test apparatus (Electrolab) to measure the friability of tablets. The tablets were then dedusted, reweighed and loss in weight was calculated.

$$\text{Friability} = \frac{W1 - W2}{W1} \times 100 \quad (4)$$

### Drug content

Ten tablets from each formulation were randomly selected and pulverized to a fine powder. A portion of powder equivalent to a single dose (8 mg) of Doxazosin mesylate was accurately weighed and assayed for the drug content using UV/Visible spectrophotometer (Shimadzu) at a wavelength of 245 nm. The mean percent drug content was calculated as an average of three determinations.

### *In vitro* disintegration time

The test was carried out using USP Tablet disintegration apparatus (Electrolab). Six tablets were placed in distilled water in six tubes respectively, maintained at 37°C and at agitation speed of 30 cycles per min.

### Wetting time

A piece of tissue paper folded double was placed in a Petri dish containing 10 ml of water. The tablet was placed on the paper, and the time for complete wetting of the tablet was measured in seconds. The method was slightly modified by maintaining water at 37°C. Wetting time corresponds to the time taken for the tablet to disintegrate when kept motionless on the tongue.

### *In vitro* dissolution study

*In vitro* dissolution studies of commercial IR product and ODT formulations has been performed using USP dissolution apparatus- II, paddle apparatus using 900 ml of 0.01 N HCL at paddle rotation of 50rpm at 37 ± 0.5°C. 10 ml of the samples were withdrawn at predetermined time intervals of 5, 10, 15, 20, 30, 45, 60 mins for a period of 60 mins and replaced with the fresh medium of 0.01 N HCL. The samples were filtered through 0.45 mm membrane filter, suitably diluted and analyzed at 245 nm using double beam UV/Visible spectrophotometer (Shimadzu Corporation, UV-1800, Japan). The content of drug was calculated using equation generated from standard calibration curve. Dissolution study was carried out for formulation F4 with least disintegration time and wetting time.[11,12]

### Formulation development

Depending on the mouth dispersion time (placebo tablets) wetting time, friability and *in vitro* disintegration test, diluent was selected. It was observed that mouth dispersion/wetting time was on higher side in F1 and F2; hence granulation of Mannitol was considered so as to improve its friability, wetting time and porosity for faster disintegration. Thus in batch F3, granulated Mannitol was used as diluent and the tablets were evaluated.

### Selection of superdisintegrant on the basis of tablet evaluation

Kollidon® CL-F, Croscarmellose sodium, Polacrilin Potassium, Polyplasdone XL were evaluated so as to get a suitable and effective superdisintegrant Table 2.

Tablets were prepared as per the formula Table 3.

### Optimization using design expert® software

Selection of disintegrant was done using the statistical software. The general factorial design was applied with two indepenent factors-Type of disintegrant and concentration of disintegrant and the three responses were-*In vitro* disintegration time, *In-vivo* dispersion time (placebo) and Wetting time. The statistical reports were then evaluated for the selection of an appropriate disintegrant. The different batches of the formulation with different type and concentration of superdisintegrants were evaluated on the basis of the tablet evaluation.

A particular disintegrant with optimum concentration was selected using general factorial design. In a full factorial design, all the factors are studied in all the possible combinations, as it is considered to be most efficient in estimating the influence of individual variables (main effects) and their interactions. In the present study, since the type of disintegrant and its concentration was to be determined with least wetting time, *in vitro* disintegration time and *in vivo* dispersion time (placebo) therefore two independent factors were considered i.e., type of disintegrant (Crospovidone-Kollidon® CL-F, Croscarmellose sodium, Polacrilin potassium and Polyplasdone®-XL) and concentration of disintegrants (5, 7.5 and 10%); whereas *In vitro* disintegration time, wetting time, *in vivo* dispersion time (placebo) were measured as responses. 12 formulations were prepared according to general factorial design. The responses were analyzed for analysis of variance (ANOVA) using Design Expert version 8.0.7.1 software. Statistical models were generated for each response parameter. The models were tested for significance. As per the investigation; reproducible batches were planned with the selected superdisintegrant. These batches were then subjected for analytical study.[13-17]

**Table 1: Formulation composition for selection of diluent**

| Formulation code | F1 (mg) | F2 (mg) |
|---|---|---|
| Doxazosin mesylate: Eudragit EPO Spray dried microspheres | 32.5 | 32.5 |
| Mannitol | 198.75 | - |
| Dextrose | - | 198.75 |
| Crospovidone (Kollidon® CL-F) | 12.5 | 12.5 |
| Peppermint flavour | 5 | 5 |
| Aspartame | 7.5 | 7.5 |
| Magnesium stearate | 1.25 | 1.25 |
| Total | 250 | 250 |

**Table 2: Formulation composition including granulated mannitol**

| Formulation code ingredients | F3 (mg) |
|---|---|
| Doxazosin mesylate: Eudragit EPO Spray dried microspheres | 32.5 |
| Granulated mannitol | 198.75 |
| Crospovidone (Kollidon CL-F) | 12.5 |
| Peppermint flavour | 5 |
| Aspartame | 7.5 |
| Magnesium stearate | 1.25 |
| Total | 250 |

### stability studies

The optimized batch was then filled in HDPE containers and then kept at 40°C ± 2°C/75% RH ± 5% in a stability chamber (Newtronic equipments) and then sampling was done initially and then every month for a period of three months.

## RESULTS AND DISCUSSION

Spray drying technique was used for the taste masking of Doxazosin mesylate by coating the drug with Eudragit EPO polymer because it requires only a one step process and can be easily controlled and scaled up. Eudragit EPO was used as a taste masking agent because it dissolves at a pH of less than five. Therefore, it does not dissolve in the buccal cavity (pH 5.8-7.4) and keeps the coated drug intact to produce good taste masking, but the polymer dissolves in the stomach (pH 1-3) to release the drug.

**Table 3: Formulation compositions for selection of superdisintegrant**

| Formulation code | Quantity per tablet (mg) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | F4 | F5 | F6 | F7 | F8 | F9 | F10 | F11 | F12 | F13 | F14 | F15 |
| Ingredients (mg) | | | | | | | | | | | | |
| Doxazosin mesylate: Eudragit EPO Spray dried microspheres | 32.5 | 32.5 | 32.5 | 32.5 | 32.5 | 32.5 | 32.5 | 32.5 | 32.5 | 32.5 | 32.5 | 32.5 |
| Granulated mannitol | 191.25 | 185 | 178.75 | 191.25 | 185 | 178.75 | 191.25 | 185 | 178.75 | 191.25 | 185 | 178.75 |
| Kollidon® CL-F | 12.5 | 18.75 | 25 | - | - | - | - | - | - | - | - | - |
| Croscarmellose sodium | - | - | - | 12.5 | 18.75 | 25 | - | - | - | - | - | - |
| Polacrilin potassium | - | - | - | - | - | - | 12.5 | 18.75 | 25 | - | - | - |
| Polyplasdone XL | - | - | - | - | - | - | - | - | - | 12.5 | 18.75 | 25 |
| Peppermint flavour | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Aspartame | 7.5 | 7.5 | 7.5 | 7.5 | 7.5 | 7.5 | 7.5 | 7.5 | 7.5 | 7.5 | 7.5 | 7.5 |
| Magnesium stearate | 1.25 | 1.25 | 1.25 | 1.25 | 1.25 | 1.25 | 1.25 | 1.25 | 1.25 | 1.25 | 1.25 | 1.25 |
| Total | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 |

### Determination of taste recognition threshold of doxazosin mesylate

'N'-Bitter taste has not been recognised by the volunteer.
'Y'-Bitter taste has been recognised by the volunteer.

All the nine volunteers could not recognize the bitter taste of Doxazosin Mesylate at 6 µg/ml. Seven out of nine can percept the bitter taste at 11 µg/ml, whereas all the nine volunteers reported that the solutions of 16 and 20 µg/ml were bitter. Thus the threshold bitterness value lies in between 6-11 µg/ml. Therefore the Doxazosin Mesylate solutions of 7, 8. 9. 10 µg/ml were prepared and the same procedure was repeated. From Table 4 the bitter taste threshold value of Doxazosin Mesylate is 9 µg/ml.

### Taste masking evaluation

The prepared microspheres were evaluated for *in-vitro* taste masking in 10 ml phosphate buffer pH 6.8. The drug release from 1:1 and 1:2 drug-polymer ratio microspheres were greater than the bitter taste recognition threshold value of Doxazosin mesylate. While excellent taste masking was achieved by 1:3 drug-polymer ratio with drug release lesser than the bitter taste threshold value of Doxazosin mesylate. Hence 1:3 ratio was selected as the taste masked microsphere.

### Drug entrapment efficiency, drug loading, yield

The yield of the spray dried microspheres was on the lower side. The low yield could be due to a smaller portion of small and light particles which escaped through the exhaust of the spray dryer during the spray-drying process. The yield of the microspheres may be further improved if the loss of particles through the exhaust of the spray dryer apparatus can be prevented Table 5.

### Thermal analysis

The thermo gram of Doxazosin mesylate shows a sharp endothermic peak at 281°C [Figure 1].

The thermo gram of microspheres also shows sharp endothermic peak at 278°C representing no significant shift in the peak in comparison to the pure drug. Thus indicating no interaction between the drug and the polymer [Figure 2].

### Particle sizing

Particle sizing done by using Motic Optical microscope. Particle sizing by optical microscopy revealed the size of microspheres which was in the range of 30-40 µm [Figure 3].

### Infrared spectroscopy

The FTIR spectrum of Doxazosin Mesylate, Eudragit EPO and spray dried microspheres of Doxazosin Mesylate-Eudragit EPO is depicted in the Figures 4-6. Doxazosin Mesylate exhibited characteristic peaks attributed to N-H stretching at 3345 $cm^{-1}$ and C=N stretching at 1593 $cm^{-1}$. FTIR spectrum of Eudragit EPO also exhibited characteristic peak attributed to C=O of Eudragit at 1730 $cm^{-1}$. The spray dried microspheres exhibited both the characteristic peaks for Doxazosin at 3345 $cm^{-1}$ and 1593 $cm^{-1}$, also for Eudragit at 1731 $cm^{-1}$.

Thus there was no significant interaction observed between drug and polymer.

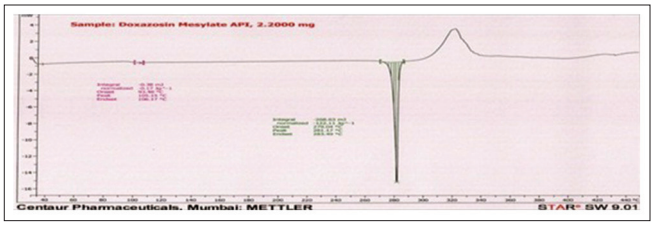


**Figure 1:** Differential scanning calorimetry thermogram of pure doxazosin mesylate

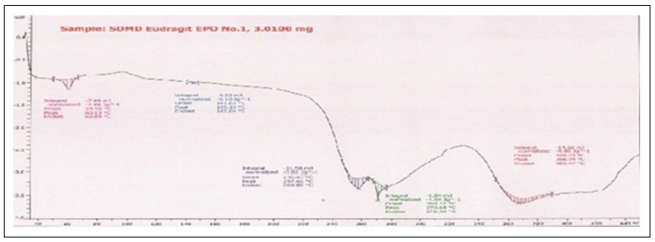


**Figure 2:** Differential scanning calorimetry thermogram of Doxazosin – Eudragit EPO spray dried microspheres

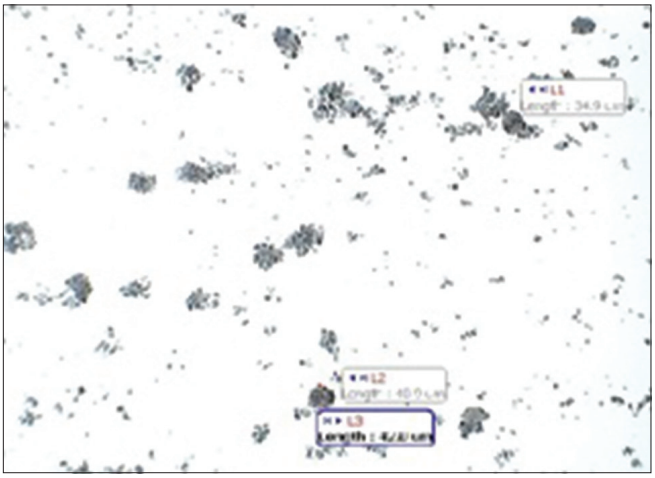

**Figure 3:** Optical microscope image with particle sizing

**Figure 4:** Fourier transform IR spectrum of doxazosin mesylate

### Scanning electron microscopy

The SEM micrographs of Eudragit microspheres are depicted in Figure 7. The microspheres prepared by spray drying were spherical in shape with small diameter. The SEM images confirmed the uniformity of the microspheres which contributed for rapid drug release from the microspheres. Thus, the objective of masking the bitter taste of Doxazosin mesylate was successfully achieved without affecting the release kinetics.

### Evaluation of tablets

*Selection of diluent*

Formulation F1 and F2 both showed higher wetting time and disintegration time and also the tablets were friable. Thus Mannitol and dextrose, both had problems of prolonged wetting time and friability. Then another batch with granulated Mannitol was produced. Mannitol was granulated with water using Rapid Mixer Granulator (Bectochem) and then dried using FluidBed Drier (Bectochem) at inlet temperature of 50-55°C, Exhaust-33°C and blower speed-1600 RPM till LOD came down to 1.08% [Table 6].

**Table 4: Results for taste recognition threshold**

| Concentration (µg/ml) | Volunteers | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| 2 | N | N | N | N | N | N | N | N | N |
| 6 | N | N | N | N | N | N | N | N | N |
| 7 | N | N | N | N | N | N | N | N | N |
| 8 | N | N | N | N | N | N | N | N | N |
| 9 | N | Y | N | Y | Y | N | N | Y | Y |
| 10 | N | Y | N | Y | Y | Y | N | Y | Y |
| 11 | Y | Y | N | Y | Y | Y | N | Y | Y |
| 16 | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| 20 | Y | Y | Y | Y | Y | Y | Y | Y | Y |

**Table 5: Results for microsphere evaluation**

| Drug-polymer ratio | Drug entrapment efficiency (%) | Drug loading (%) | % yield |
|---|---|---|---|
| 1:1 | 93.5 | 45.3 | 57.1 |
| 1:2 | 95 | 29.7 | 53.4 |
| 1:3 | 98.1 | 22.1 | 56.2 |
| 1:4 | 94.1 | 16.7 | 50.8 |
| 1:5 | 101.4 | 14.2 | 53.5 |

Thus from Table 7, it is clear that usage of granulated Mannitol has decreased friability, disintegration time and Mouth dispersion time/Wetting time. Granulated Mannitol was selected as the diluent and content uniformity was also acceptable with *in vivo* dispersion time (placebo) on lower side i.e., below 40 secs.

### Selection of super disintegrant

It is observed from the Table 8 that the Superdisintegrant-Crospovidone (Kollidon CL-F) with the concentration of 5% w/w is the most effective for fast disintegration and decreased mouth dispersion time (wetting time).

*Selection of superdisintegrant*

The *P* value/Prob>F was found to be 0.0312 which is an indication that the model selected was significant since the *P* value/Prob>F was found to be below 0.05. This indicates that the type and concentration of disintegrants affect the *in vitro* disintegration time, wetting time and *in vivo* dispersion time. Thus from 3D graph plots its quite clear that 5-7.5 %w/w Kollidon® CL-F as super disintegrant gives the best desired results with lower *in vitro* disintegration time, wetting time and *in vivo* dispersion time. Figures 8-10

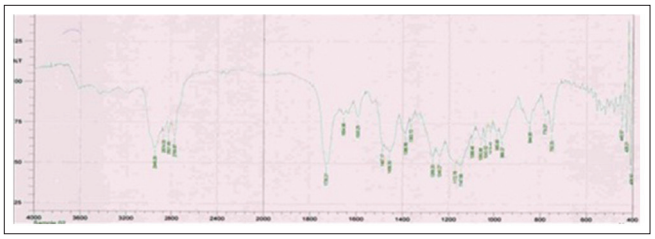

**Figure 5:** Fourier transform IR spectrum of eudragit EPO

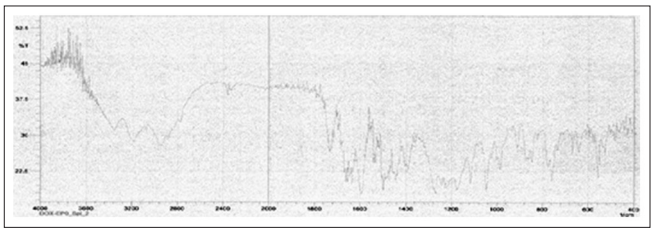

**Figure 6:** Fourier transform IR spectrum of spray dried microspheres of doxazosin mesylate and eudragit EPO

**Table 6: Results for formulations F1 and F2**

| Formulation code | Hardness(*N*) (*n*=10) Mean±SD | Friability (%) (*n*=25) | *In vitro* disintegration time (sec) (*n*=6) Mean±SD | Wetting time (sec) (*n*=6) Mean±SD |
|---|---|---|---|---|
| F1 | 37±3.01 | 0.75 | 32±2.15 | 70±3.2 |
| F2 | 35±3.23 | 1.2 | 36±2.55 | 84±2.74 |

**Table 7: Results for formulation F3 evaluation**

| Formulation code | Hardness (*N*) (*n*=10) Mean±SD | Friability (%) (*n*=25) | *In vitro* disintegration time (sec) (*n*=6) Mean±SD | Wetting time (sec) (*n*=6) Mean±SD | Drug content (%) Mean±S.D. | *In vivo* disperse-on time (placebo) (*n*=6) |
|---|---|---|---|---|---|---|
| F3 | 38±2.15 | 0.46 | 18±1.84 | 24±2.1 | 98.1±1.41 | 38 secs |

gives a graphical representation which is obtained from design expert® software and clearly defines that the superdisintegrant-Kollidon® CL-F is the most effective superdisintegrant with lower *in-vivo* dispersion time (placebo), wetting time and *in vitro* disintegration time. Particle size of this grade of crospovidone is 20-40 µ which gives it an excellent disintegration power as compared to the other disintegrants used in this study.

Thus the tablet formulations were optimized using general factorial design. The outcomes for response parameters, i.e., Disintegration time, Wetting time, *In vivo* dispersion time (Placebo) were subjected to regression analysis, and statistical models were found to be significant. The high values of correlation coefficient for Disintegration Time, Wetting Time, *In vivo* dispersion time (Placebo) indicate a good fit, i.e., good agreement between the dependent and independent Variables. The F value in the ANOVA [Table 9] is the ratio of model mean square to the appropriate error mean square. The larger the ratio, the larger the F value and the more likely that the variance contributed by the model is significantly larger than random error. If the F ratio-the ratio of variances-lies near the tail of the <F> distribution, then the probability of a larger F is small and the variance ratio is judged to be significant. Usually, a probability less than 0.05 is considered significant. The model F value of 42.42 for Disintegration time, 2233.09 for wetting time and 78.89 for *in vivo* dispersion time and high $R^2$ values suggest that these models are significant. There is only 0.01% chance that a 'model F value' this large could occur due to noise. Values of 'p' less than 0.0500 indicate that model terms are significant. In this case, models generated for Disintegration time, wetting time and *in vivo* dispersion time are significant. As there are no insignificant terms, model reduction is not required. Adequate precision measures the signal-to-noise ratio. A ratio greater than four is desirable. The ratios of 21.912, 132.046 and 106.232 respectively, for

**Table 8: Results for evaluation of Doxazosin mesylate orally disintegrating tablets tablets**

| Formulation code | *In vitro* disintegration time (secs) *n*=6 Mean±SD | Wetting time(secs) *n*=6 Mean±SD | *In vivo* dispersion time (placebo) (secs) *n*=2 (Mean) |
|---|---|---|---|
| F4 | 11±1.04 | 21±2.08 | 31 |
| F5 | 11±1.1 | 19±0.57 | 29 |
| F6 | 12±1.3 | 18±0.55 | 29 |
| F7 | 14±2.08 | 45±0.57 | 54 |
| F8 | 13±1.2 | 35±1.52 | 48 |
| F9 | 17±1.4 | 52±2 | 56 |
| F10 | 45±1.05 | 75±4.04 | 70 |
| F11 | 55±3.11 | 87±2.64 | 72 |
| F12 | 59±3.24 | 91±2.64 | 74 |
| F13 | 22±1.2 | 49±2.64 | 57 |
| F14 | 24±1.88 | 46±2.6 | 53 |
| F15 | 26±1.7 | 51±2.8 | 51 |

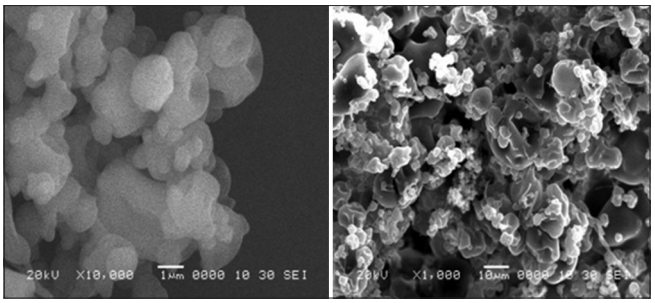

**Figure 7:** Scanning electron microscopy micrographs of spray dried microspheres

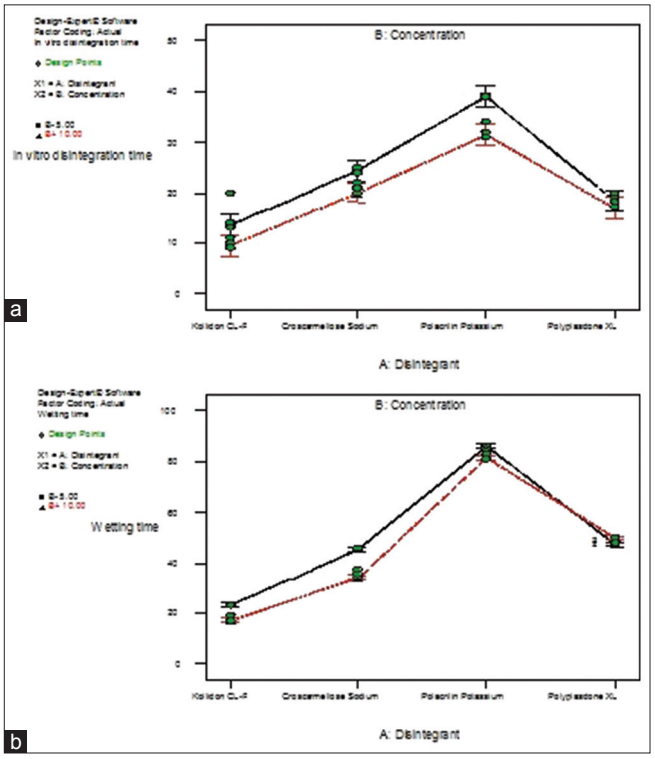


**Figure 8:** (a) Plots for *In vitro* disintegration time and (b) Plots for Wetting time

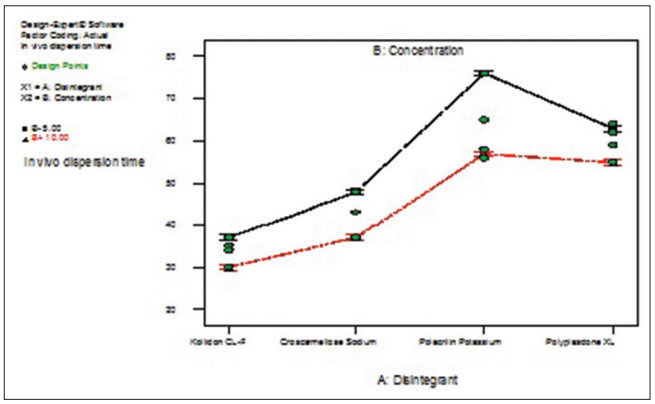


**Figure 9:** Plots for *in vivo* dispersion time

Disintegration time, wetting time and *in vivo* dispersion time indicate an adequate signal for each. These models

can be used to navigate the design space. It was observed that disintegration time, wetting time and *in vivo* dispersion time was dependent on both factors. This was observed from graph plots [Figures 8a, b and 9].

Thus from the statistical parameters and plots it can be concluded that the super disintegrant-Crospovidone (Kollidon® CL-F) is the most effective disintegrant at concentration 5% with granulated Mannitol as diluent.

### *Wetting time*

Formulation F4 with super-disintegrant Kollidon® CL-F had the lowest wetting time [Figure 10] as compared to other superdisintegrants.

### *In vitro* dissolution study

*In vitro* dissolution studies of commercial product (Doxacard, Cipla) released more than 80% of drug in 15 minutes in 0.01 N HCl. The formulation F4 ODT showed faster release than the marketed IR product. Dissolution was carried out of both the strengths of Doxazosin ODT i.e., 4 and 8 mg and compared with the marketed IR product of lower strength and an IR tablet prepared using the uncoated drug. The formulation F4 was selected because it had least quantity of superdisintegrant with minimum disintegration time.

### Stability studies

There was no significant change in the physical characteristics of the tablet and the dissolution was also unaffected [Figures 11-13].

## CONCLUSION

The present study was an attempt to develop a patient friendly dosage form for a potential drug candidate-Doxazosin Mesylate. This drug has some ideal characteristics for it to be administered in the form of orally disintegrating tablets (ODT). This drug is for the treatment of BPH that occurs in geriatric population who generally have problem of Dysphagia. ODT might solve the problem and be a patient friendly dosage form. The half-life of this drug is 22 hours which allows it to be given once daily. These are some of the ideal properties of Doxazosin for it to be given as an ODT. But for an ODT, palatability is an important criterion. This drug-Doxazosin mesylate had intense bitter taste so it was a bit difficult to go ahead with ODT formulation. Thus taste masking was required to be performed. For the taste to be recognized, first the drug enters the saliva and then comes in contact with the taste buds. An attempt was made to create a barrier between the drug and the saliva so as to mask the bitter taste. For this a polymer coating was found to be the effective taste masking method but the polymer was required which would serve as a barrier between the saliva and the drug at the same time it would also not hinder the release of the drug. Polymer was supposed to resist the saliva at pH 6.8 and dissolve in the gastric pH. Thus polymer Eudragit® E series was found to be the polymer which sufficed the requirement and was a reverse enteric polymer suitable for taste masking. Polymer Eudragit® EPO was then coated using spray drying technique which was found to be the most feasible method since it

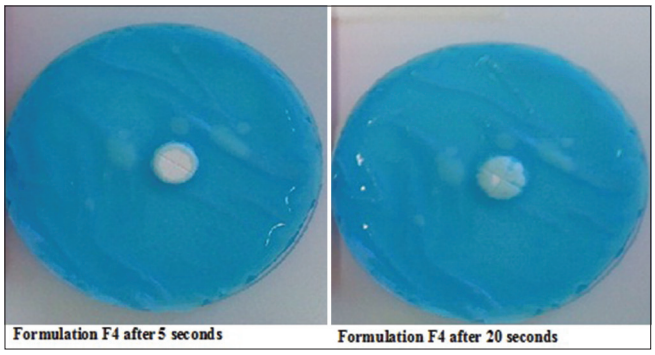


**Figure 10:** Wetting time study

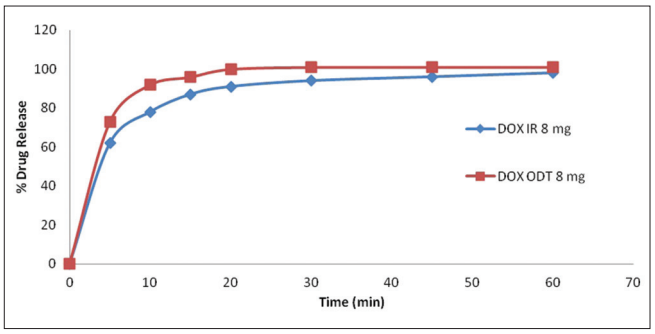


**Figure 11:** *In vitro* dissolution profile comparison of 8 mg ODT and IR Tablet in 0.01 N HCl

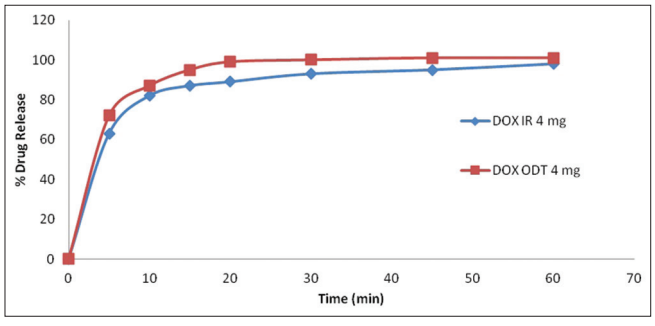


**Figure 12:** *In vitro* dissolution profile comparison of 4 mg ODT and IR Tablet in 0.01N HCl

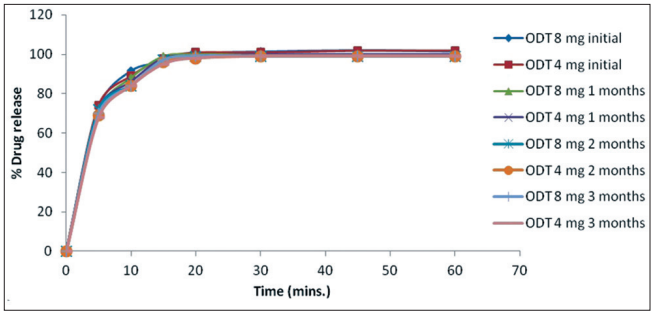


**Figure 13:** *In vitro* dissolution profile of 4 mg and 8 mg ODT (40°C/75%RH) after 3 months in 0.01 N HCl

**Table 9: ANOVA for selected statistics model**

| Response model | Sum of squares | Mean square | F value | *P* value | $R^2$ | Adeq. Precision |
|---|---|---|---|---|---|---|
| Disintegration time | 1691.46 | 153.77 | 42.42 | <0.0001 | 0.9849 | 21.912 |
| Wetting time | 12976.73 | 1622.09 | 2233.09 | <0.0001 | 0.9992 | 132.046 |
| *In vivo* dispersion time (Placebo) | 4509.13 | 409.92 | 78.89 | 0.0312 | 0.9990 | 106.232 |

**Table 10: Stability report of optimized F4 formulation**

| Parameters | Initial | 1 month | 2 months | 3 months |
|---|---|---|---|---|
| Appearance | Whit, flat on both sides with beveled edges | No change | No change | No change |
| Hardness (*N*) | 36 | 33 | 32 | 32 |
| *In vivo* dispersion time (placebo) | 39 | 42 | 43 | 42 |
| Friability (%) | 0.464 | 0.487 | 0.501 | 0.511 |
| Drug content (%) *N*=3, mean±S.D | 98±1.21 | 96.9±1.41 | 97.3±1.48 | 96.7±1.38 |

was a one step process and also scaling up of the process was feasible. Thus taste masking was successfully achieved using Eudragit® E PO polymer and spray drying technique. Then the next step was the formulation development of an ODT. Granulated Mannitol was found to be the most effective diluent with lesser friability, sufficient hardness and faster *in vivo* dispersion time (placebo). Since official disintegration test does not give exact disintegration time in relation to *in vivo* therefore placebo batches of all the formulation were prepared and *in vivo* dispersion time was noted down. Thus, this *in vivo* dispersion time (placebo) became an important factor in the formulation development. Then the heart of an ODT formulation i.e., superdisintegrant was selected using appropriate statistics obtained by Design Expert® 8.0.7.1 software which showcased that the superdisintegrant Kollidon® CL-F as the most effective superdisintegrant with least disintegration, wetting and *in vivo* dispersion time [Table 8]. It was the smaller particle size grade (20-40 μ) which boosted its disintegration property. Final optimized formulation had a good mouth feel and disintegrated within 40 seconds in mouth (placebo tablets). This optimized formulation also had comparable release and in fact a bit faster release than the marketed IR product. The formulation was also found to be stable under accelerated stability conditions of 40°C ± 2°C/75% ± 5% RH for three months. Thus an attempt was made to mask the bitter taste of drug. The results conclude that the spray drying of the drug with the polymer-Eudragit® EPO has not affected its release. Hence an attempt for development of patient friendly dosage form with the ideal drug candidate could be an alternative to the marketed IR product with good palatability and faster release [Table 10].

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