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# FORMULATION AND EVALUATION OF OFLOXACIN ALGINATE MICROSPHERES FOR LUNGINFECTION IN THE FORM OF DRY POWDER INHALER

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## ABSTRACT

The present research work is focussed on the formulation and evaluation of ofloxacin alginate microspheres for lung infection in the form of dry powder inhaler. Microspheres containing ofloxacin with a mean diameter of 2- 5 um were prepared by the spray drying of ofloxacin alginate micreosphers. The fine particle fraction (FPF) from Ofloxacin measured by a twin-stage impinger was unexpectedly found to be zero, although scanning electron microscopy showed that the drug coated the entire microsphere. coating the microspheres with sodium alginate (1%–2%) significantly increased ($p < 0.05$, $n = 5$) the FPF of SS (11.4%–15.4%), whereas coating with β Cyclodextrin had a similar effect (FPF = 11.3 ± 1.1%), The force of adhesion (by atomic force microscopy) between the Ofloxacin microspheres was reduced from 301.4 ± 21.7 nN to 110.9 ± 30.5 nN and The presence of sodium alginate and β Cyclodextrin on the Ofloxacin microspheres (detected by Scaning electron spectroscopy) affected the detachment of due to strong adhesion between the two, presumably due to capillary forces acting between them. Precoating the microspheres with excipients increased the FPF significantly by reducing the drug–carrier adhesion. © 2011 Wiley Periodicals, Inc. and the American Pharmacists Association.

**Keywords**: Microspheres, dry powder inhalers, materials and methods,Formulation, Dry Powder Inhaler.

## INTRODUCTION

Microspheres are characteristically free flowing powders consisting of spherical particles of size less than 1000 µm.Ofloxacin is chemically 7-fluoro-2-methyl-6-(4-methylpiperazin-1-yl)-10-oxo-4-oxa-1 azatricyclo [7.3.1.05,13]trideca-5(13),6,8,11-tetraene-11-carboxylic acid Ofloxacin is bactericidal and its mode of action depends on blocking of bacterial DNA replication by binding itself to an enzyme called DNA gyrase, which allows the untwisting required to replicate one DNA double helix into two. Ofloxacin acts on DNA gyrase and toposiomerase IV, enzymes which, like human topoisomerase, prevents the excessive supercoiling of DNA during replication or transcription, Sodium alginate is chemically 3-(6-carboxy-3,4-dihydroxy-5-phosphanyloxan-2-yl)oxy-4,5- dihydroxy-6-phosphanyloxyoxane-2-carboxylic acid. Sodium alginate can be used as a flavorless gum. It is used by the foods industry to increase viscosity and as an emulsifier. It is also used in indigestion tablets and the preparation of dental impressions.β Cyclodextrin is a Absorption enhancer, controlled release, permeation enhancer, Enhances solubility of drugs, Enhances bioavailability of drugs, enhances stability of drugs, reduced gastric ulceration.

## MATERIALS AND METHODS

### Apparatus and Instruments

Spectroscopic measurements were carried on FT-IR spectrophotometer.(Jasco 4000), U.V Visible Spectrophotometer (Shimadzu 1800). Electronic Weighing Balance (United Weigh Scale), Spray Dryer (Jay Instrument), Ultrasonic Bath Sonicator (Expo Hi-Tech) were used during the study.

**Chemicals and Reagents**

Ofloxacin was generously obtained as a gift sample from Emcure pharma (Pune, India). Sodium Alginate was kindly obtained from Evonik India Pvt ltd (Mumbai, India). and Beta-Cyclodextrin obtained from Akums drugs & pharma Ltd (Mumbai,India), Lactose was obtained from Orchev pharma Pvt. Ltd.(Pune,India)

**Formulation Development Of Microspheres:**

Preparation Of Microspheres**:** Ofloxacin microspheres were prepared by spray drying method. The drug is dissolved in distilled water with constant stirring. This drug solution was then sonicated for 20 mins to dissolve the drug completel. The polymers were then dissolve separately in distilled and allowed it to sonicate for 20 mins. Then these polymeric solutions mixed together with constant stirring. After this, the drug solution was added slowly into the polymeric solution with constant stirring and sonicated for 15 mins and the solution was filtered through wattman filter paper using vaccum filtration. The final solution was then spray dried and resulted microspheres were collected.

**Table 1 : Formulation Batches Of Microspheres**

| Sr. No. | Batch Code | Drug (g) | Sodium Alginate(g) | B-Cyclodextrin(g) | D : SA : BCD |
|---|---|---|---|---|---|
| 1 | FF1 | 1 g | 1 g | 1 g | 1:1:1 |
| 2 | F2 | 1 g | 1 g | 2 g | 1:1:2 |
| 3 | F3 | 1 g | 2 g | 1 g | 1:2:1 |
| 4 | F4 | 1 g | 5 g | 1 g | 1:5:1 |
| 5 | F5 | 1 g | 1 g | 1 g | 1:1:1 |
| 6 | F6 | 1 g | 1 g | 2 g | 1:1:2 |
| 7 | F7 | 1 g | 0.5 g | 1 g | 1:0.5:1 |
| 8 | F8 | 1 g | 1 g | 1 g | 1:1:1 |

**Formulation Development Of Dry powder inhaler:**

**Manufacturing process :**

An accurately weighed amount of ofloxacin microspheres was mixed separately with Lactose in geometric progress and passed through 60# mesh and filled in to size "3" hard gelatin capsules withfill weight of 50 mg per capsules.

**Preparation of the dry powder inhalers with fine lactose:**

Ofloxacin microspheres formulations were prepared with fine lactose with 50 mg fill weight

**UV Spectrum Of Ofloxacin:**ofloxacin of about 100 mg was dissolved in sufficient amount of 0.1 N HCL in a 100ml volumetric flask. The volume was made up with 0.1N HCL to get concentration 1000 µg/ml. From this solution 10 ml was withdrawn and diluted to 100 ml with 0.1 N HCL to get the working stock solution of concentration of 100µg/ml. This drug solution (100µg/ml) was scanned in UV-Visible Spectrophotometer in thewavelength range of 200-400 nm against the reagent blank. Wavelength maxima (λmax) were determined from the spectra of respective drug and were used for the further experimentation.

**Construction Of Calibration Curve For Ofloxacin:** UV method: ofloxacin of about 100 mg was dissolved in sufficient amount of 0.1N HCL in a 100ml volumetric flask. The volume was made up with 0.1N HCL to get concentration 1000 µg/ml. From this 10 ml was withdrawn and diluted to 100 ml with 0.1N HCL to get workingstock solution of concentration of 100 µg/ml. Different concentrations were prepared in the range of 2-10 µg/ml by appropriately diluting the stock solution with 0.1N HCL. The absorbance values were measured at 294 nm against the blank and calibration curve was constructed.

**Fourier Transmission Infrared (FTIR) Spectroscopy:** Fourier transform instruments determine the absorption spectrum for a compound in the common range of 4000 to 400 cm-1.

**Melting Point:** The melting point of the substance is defined as the temperature at which solid phase exists in equilibrium with its liquid phase. This property is of great value as characterization tool since information canbe used for compound identification or in an estimation of purity. The melting point of ofloxacin was determined by capillary method using the melting point apparatus. Drug was filled in glass capillary tube which was sealed at one end that was attached with thermometer. The drug containing capillary with thermometer was dipped in liquid paraffin and progress in temperature was monitored. Inside the melting point apparatustemperature at which drug starts melting are recorded.

**Solubility:** The spontaneous interaction of two or more substance to form a homogenous molecular dispersion is called as solubility.

**In Vitro Drug Release Study.**

Drug release from spray dried ofloxacin microspheres was carried out using modified dissolution method. The phosphated buffered solution of pH 7.4 was prepared. The microspheres equivalent to 50 mg of drug was suspended in dialysis tubes containing the buffer. The tubes were tied to the paddle, operated at 90 cycles/min at 37˚C for 7 hrs. At predetermined intervals of time, 5 ml of the sample waswithdrawn and analyzed for drug content at 294 nm using UV-visible spectrophotometer following suitable dilutions. The same amount of fresh media was replaced after each sample withdrawal.

**In Vitro Skin Permeation Study (Diffusion Study)**

The permeation study spray dried formulation was carried out across the rat abdominal skin. I carried out this study using rat abdomen skin as a physiological model. The abdominal skin of the rat was excised after anaesthetizing and sacrificing. The surface hair of the skin and adhered epidermal tissues were removedcarefully without damaging the skin. Then the skin was mounted on the donor compartment of the diffusioncell. The receptor medium used was 7.4 phosphate buffer solution. The diffusion was carried out at 37 ˚C and at
50 rpm for 6 h. The 1 mL samples were removed periodically and estimated the drug content spectro photometrically at 294 nm.

**Evaluation Of MicrospheresBulk Density-**
Bulk density is a property of powders, granules, and other "divided" solids, especially used in reference to mineral components, chemical substances, ingredients, or any other masses of corpuscular or particulate matter. It is defined as the mass of many particles of the material divided by the total volume they occupy. The total volume includes particle volume, inter- particle void volume, and internal pore volume. Bulk density is not an intrinsic property of a material; it can change depending on how the material is handled.

Bulk density = mass/volume

**Angle Of Repose-**

The angle of repose, or critical angle of repose of a granular material is the steepest angle of descent or dip relative to the horizontal plane to which a material can be piled without slumping. At this angle, the material on the slope face is on the verge of sliding. The angle of repose can range from 0° to 90°.

**Porosity**-Porosity or void fraction is a measure of the void spaces in a material, and is a

fraction of the volume of voids over the total volume, between 0 and 1, or as a percentage between 0% and 100%. Strictly speaking, some tests measure the "accessible void", the total amount of void space accessible from the surface.

**Tapped Density-**

The taapped density is obtained by mechanically tapping a graduated cylinder containing the sample until little further volume change is observed.

**Carr's Index**

The Carr index is an indication of the compressibility of a powder.The Carr index is calculated by the formula ,
C = (bulk volume- tapped volume/ bulk volume) × 100

**Hausner's Ratio**

It is a ratio of tapped density and a bulk density.HR = Tapped density/ Bulk density

**Determination Of % Yield**

The % yield of each formulation was determined according to total weight of ofloxacin and polymers to thetotal recoverable final weight of microsphere.

**Drug Content**

Microspheres (50mg) were triturated with 10 ml of water. Allowed to stand for 10 min with occasional stirring and methanol was added to produce 100 ml volume. After suitable dilutions sample were measured at 294 nm and the drug content was determined from standard plot.

**Drug Loading (%)**

Drug loading is calculated by total amount of drug used to the total recoverable final weight of microsphere.

**Entrapment Efficiency (%)**

Entrapment efficiency gives the % of drug that is successfully entrapped/adsorbed into

microspheres. It is calculated by formula-

EE% = actual drug content / theoretical drug content

**Particle Size Distribution**

The particle size distribution performed by using simple microscope at laboratory level.

**Evaluation of Dry Powder Inhaler**

**Mass Median Aerodynamic Diameter** (MMDA) is defined as the diameter at which 50% of the particles by mass are larger and 50% are smaller. MMDA can be determine by plotting, on log probability paper, the percentage of a mass less than the stated aerodynamic diameters versus the a aerodynamic diameters. The MMDA is taken as the intersection of the line with 50% cumulative percent.

**Geometric Standard Deviation** is a measure of the spread of an aerodynamic particle size distribution. Typically calculated as follows:

$$GSD = (d84/d16)1/2$$

Where d84 and d16 represen the diameter at which 84% and 16% of the aerosol mass are contained, respectively, in diameters less than these diameters.

(Note:- The geometric standard deviation (GSD) and mass median aerodynamic diameter (MMAD) were determined using an online MMAD calculator.)

**Emitted Dose**: Drug emitted dose (ED), defined as the percent of microspheres exiting the DPI, which can be determined by subtracting the amount of microspheres remaining in the DPI from the initial mass of microspheres loaded.

Emitted dose (ED) = total particle mass on all stages/initial particle mass × 100.

**FPF - Fine Particle Fraction** : The drug fine particle fraction (FPF5µm/ED) is defined as the percentage of the emitted dose with aerodynamic diameters smaller than 5 µm. This can be calculated via interpolation of the % mass less than 5 µm on a plot of the cumulative percentage mass verses cutoff diameter of the respective stages of the cascade impactor.

Fine particles dose (FPD) = mass of particles on stages 2 through 7;

Fine particle friction (FPF) = fine particle dose/initial particle mass × 100

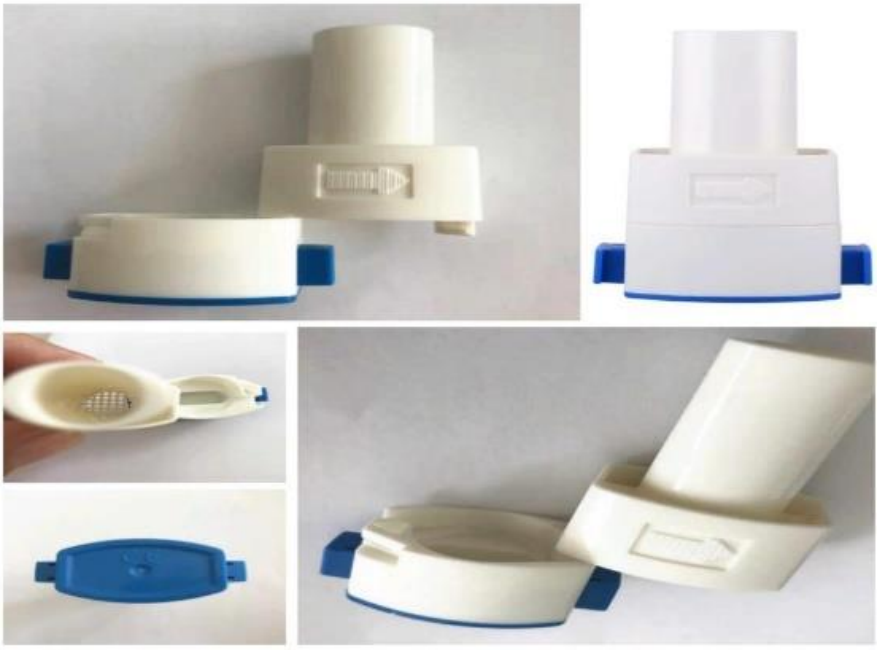


**Figure 1 : Dry Powder Inhaler Device**

## RESULTS AND DISCUSSION :

- **Identification of drug**

The sample of ofloxacin was studied for its organoleptic properties like odour and colour. The result isshown in following table**.**

**Table 2 : Identification of drug**

| **Identification Test** | **Observed Result** | **Reported Result** |
|---|---|---|
| Appearance | Pale Yellow Powder | Pale Yellow Powder |
| Odour | Pleasant | Pleasant |
| Taste | Bitter | Bitter |
| Loss on drying(%w/w) | Not more than 0.20 | 0.17 |

| | | |
|---|---|---|
| Sulphated ash (%w/w) | Not more than 0.10 | 0.05 |
| Heavy metals (in ppm) | Not more than 10 | Less than 10 |

- **UV spectrum of ofloxacin:**

The solution of ofloxacin in 0.1 N HCL was found to exhibit maximum absorption λmax at 294 nm afterscanning in the r ange of 200-400 nm.

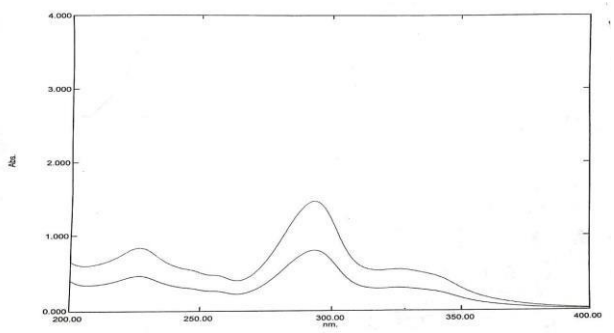
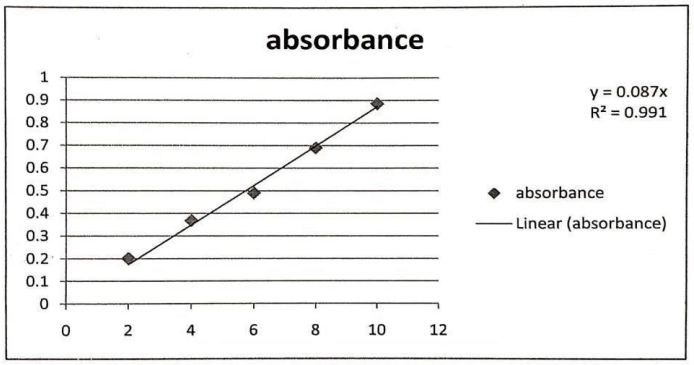



**Figure 2: Uv Spectrum of Ofloxacin**

- **Calibration curve of ofloxacin:**

UV method: The calibration curve for ofloxacin drug was determined in 0.1 N HCL



| **Conc (µg/ml)** | **absorbance** |
|---|---|
| 2 | 0.201 |
| 4 | 0.368 |
| 6 | 0.590 |
| 8 | 0.690 |
| 10 | 0.886 |

**Figure 3: Calibration Curve of Ofloxacin**

- **Fourier Transmission Infra-red Spectroscopy (FTIR):**

The identity of drug was confirmed by comparing IR spectrum of drug with reported spectrum of Ofloxacingives the functional groups

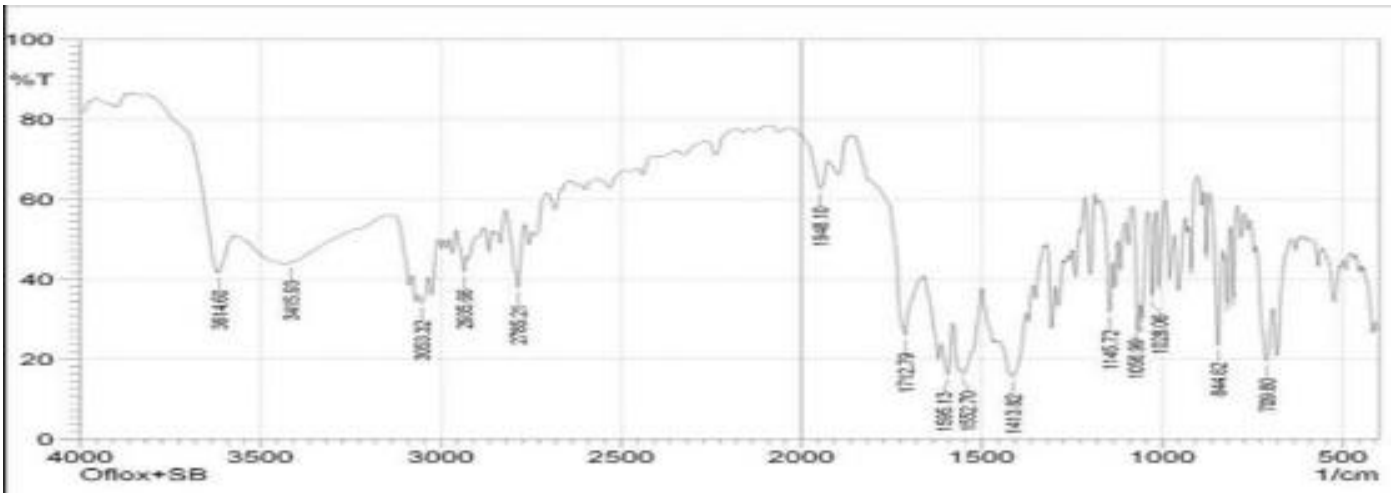



**Figure 4: FTIR Of Ofloaxacin**

**Table 3 : FTIR values of Ofloxacin**

| **Wavelength ($cm^{-1}$)** | **Functional group** |
|---|---|
| 2110 $cm^{-1}$ | C-H(stretch) |
| 1723 $cm^{-1}$ | C=0(stretch) |
| 3540 $cm^{-1}$ | N-H (stretch) |
| 3361 $cm^{-1}$ | 0-H(stretch) |
| 1240 $cm^{-1}$ | C-O (stretch) |

- **Melting point:**
  The melting point of ofloxacin was found to be **250–255 °C**, thus indicating the purity of obtained drugsample.

**Micromeritic properties of microspheres**

**Table 4 : Micromeritic properties of Drug**

| Batch | Flow Rate (gm/cc) | Bulk Density (gm/cc) | Tapped Density (gm/cc) | Carr's Index (%) | Angle Of Repose | Hausner's Ratio | % Porosity |
|---|---|---|---|---|---|---|---|
| F3 | 0.011 | 0.252 | 0.2645 | 13.95 | 34.49 | 1.175 | 13.5 |

- **Particle size analysis**

**Microscopic Method**

The following image was taken by a smart phone which shows micro sized particles of ofloxacin. Ofloxacin microspheres was visualized by simple compound microscope forthe surface morphology. The image shows that formulation contains microspheres with smooth surface. The experimental results showed that the microspheres have an average particle size of 11.32 microm. The drug loading and loading efficiency were (59.33 and 95.17%) respectively.

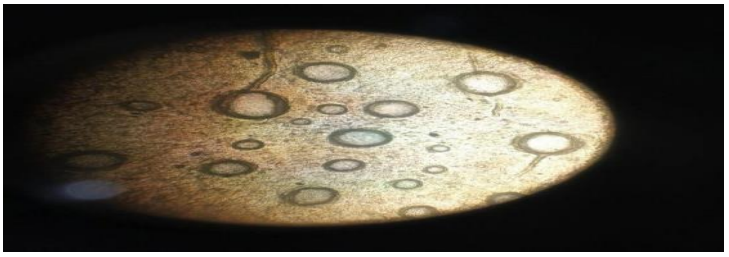


**Figure 5: Microscopy of Ofloxacin**

- **Scanning Electron Microscopy (SEM)**

Surface characteristics of the microspheres was analysed by scanning electron microscopy (SEM) method. For this testing the ZEISS Scanning electron microscope, (DIYA LABS, airoli) was used with different resolutions. Generally, spherical shape particles are more phagocytosed than elongated/rode shaped particles . The particle morphology of the optimized LVX-loaded microspheres is shown in Figure. It is obvious that LVX-loaded microspheres have a relatively smooth surface with spherical geometry. This spherical geometry is anticipated to facilitate the uptake of the optimized microsphere by alveolar macrophages. In addition, no signs of aggregation were observed among the formulated microspheres, which could aid the efficientaerosolization of particles as DPIs.

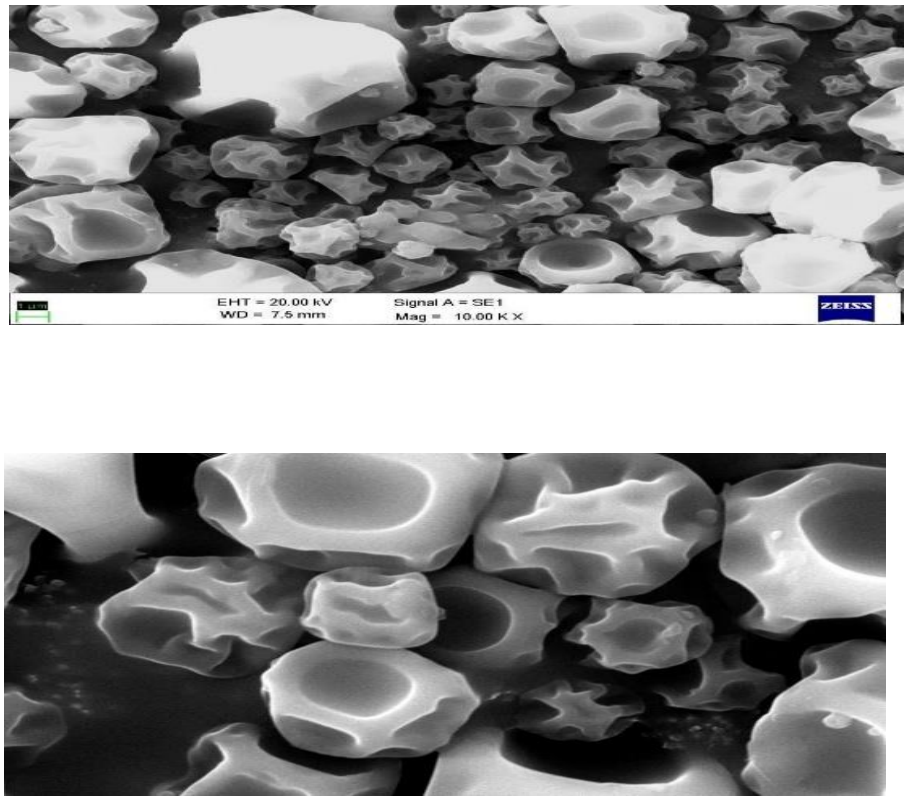



**Figure 6: Scanning Electron Microscopy.**

- **%Yield, Drug Loading,Drug Content And Entrapment Efficiency**

The results are summerised in table no.

The batch no. F3 shows better result having more entrapment efficiency than other batches

**Table 5 : Evaluarion Of Microspheres**

| Batch Code | D : SA : BCD | Drug Loading (%) | % Yield | Drug Content (%) | Entrapment Efficiency (%) |
|---|---|---|---|---|---|
| **F1** | 1:1:1 | 41.66 | 80 | 54.37 | 85 |
| **F2** | 1:1:2 | 40.65 | 74 | 66.96 | 83.16 |
| **F3** | **1:2:1** | **59.33** | **75** | **79.12** | **95.17** |
| **F4** | 1:5:1 | 61.52 | 73.2 | 80.15 | 94.16 |
| **F5** | 1:1:1 | 58.82 | 85 | 55.75 | 67.81 |
| **F6** | 1:1:2 | 52.63 | 76 | 62.45 | 88.50 |
| **F7** | 1:0.5:1 | 46.66 | 60 | 46.48 | 60.20 |
| **F8** | :1:1 | 51.01 | 68 | 50.18 | 71.12 |

- **Release Kinetics**

**In Vitro Drug Release Study (Dissolution Study)**

**Table 6 : Dissolution Studies of all Batches Showing % Drug Release.**

| TIME (hrs) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 |
|---|---|---|---|---|---|---|---|---|
| **1** | 2.19±0.57 | 2.2±0.51 | **7.683**±0.50 | 3.51±0.47 | 2.15±0.48 | 3.02±0.51 | 3.51±0.55 | 2.81±0.57 |
| **2** | 2.82±075 | 3.52±0.57 | **10.141**±0.71 | 4.01±0.55 | 3.84±0.54 | 2.15±0.57 | 2.45±0.74 | 2.55±0.6 |
| **3** | 5.25±0.84 | 6.34±0.60 | **13.667**±0.87 | 7.945±0.74 | 6.874±0.74 | 6.95±±0.67 | 6.96±0.91 | 5.56±0.87 |
| **4** | 8.85±0.94 | 10.65±0.67 | **18.151**±0.94 | 12.561±0.91 | 11.51±0.91 | 9.62±1.48 | 7.52±1.05 | 6.72±1.05 |
| **5** | 13.71±1.05 | 16.14±1.10 | **33.645**±1.08 | 18.124±1.15 | 17.95±1.20 | 18.26±1.74 | 15.26±1.30 | 12.26±1.45 |
| **6** | 20.31±1.47 | 23.5±1.48 | **49.658**±1.30 | 25.145±1.65 | 24.52±1.64 | 23.84±1.70 | 20.84±1.47 | 19.44±1.65 |
| **7** | 27.81±1.61 | 32.28±1.45 | **59.797**±1.47 | 35.65±1.79 | 34.42±1.71 | 33.26±1.79 | 31.26±1.66 | 29.46±1.71 |
| **8** | 36.97±1.74 | 42.86±1.70 | **77.671**±1.66 | 47.15±1.63 | 46.95±1.85 | 45.32±2.21 | 41.32±2.03 | 39.42±1.99 |
| **9** | 47.79±1.95 | 55.55±1.85 | **85.121**±2.03 | 60.15±2.21 | 59.12±1.99 | 58.36±2.84 | 52.36±2.87 | 50.46±2.21 |
| **10** | 60.64±2.01 | 70.05±1.99 | **94.254**±2.55 | 75.125±2.29 | 72.54±2.05 | 74.96±2.97 | 70.96±2.99 | 68.96±2.79 |

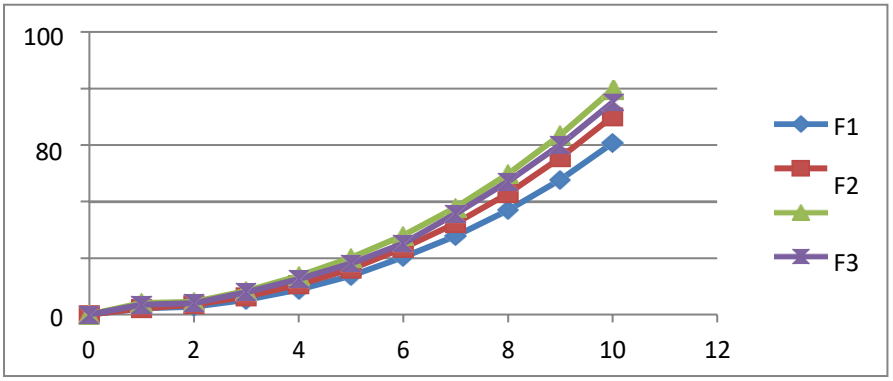



**Figure 7: In vitro drug release profile (F1-F4)**

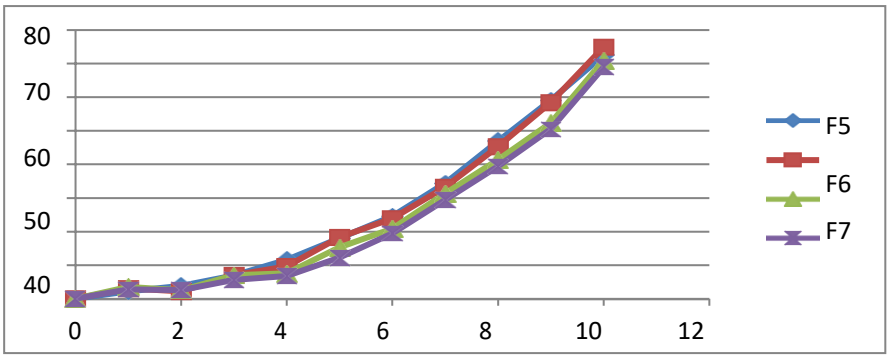



**Figure 8: In vitro drug release profile (F5-F8)**

**In vitro skin permeation study (diffusion study)**

**Table 7 : Studies of all Batches Showing % Drug Release**

| TIME | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 |
|---|---|---|---|---|---|---|---|---|
| **1** | 1.19±0.27 | 2.1±0.47 | **3.73±0.27** | 3.91±0.24 | 3.45±0.21 | 3.12±0.12 | 3.71±0.4 | 1.81±0.48 |
| **2** | 2.45±0.24 | 3.58±0.47 | **4.14±0.23** | 4.851±0.45 | 5.44±0.54 | 4.85±0.32 | 5.59±0.3 | 2.75±0.37 |
| **3** | 4.25±0.36 | 5.44±0.71 | **7.02±0.75** | 8.65±0.71 | 7.274±0.8 | 7.55±0.56 | 5.96±0.5 | 5.46±0.54 |
| **4** | 8.48±0.49 | 9.85±0.72 | **12.67±1.02** | 11.61±0.9 | 10.51±1.0 | 9.82±1.09 | 8.42±1.0 | 8.12±1.05 |
| **5** | 11.41±0.5 | 15.24±1.0 | **21.45±1.44** | 17.14±1.2 | 18.25±1.0 | 17.46±1.6 | 16.76±1. | 11.26±1.21 |
| **6** | 19.13±1.06 | 21.60±1.41 | **28.67±1.65** | 26.45±1.4 | 26.82±1.1 | 21.44±1.2 | 22.54±1. | 18.74±1.45 |
| **7** | 25.71±1.42 | 31.48±1.80 | **39.40±2.05** | 34.65±1.96 | 32.42±2.0 | 30.26±2.1 | 33.46±2. | 32.46±2.85 |
| **8** | 34.45±1.53 | 40.46±2.03 | **50.753±2.1** | 45.15±2.05 | 44.95±2.0 | 47.32±2.1 | 46.52±2. | 45.42±2.25 |
| **9** | 45.49±1.67 | 54.55±2.18 | **62.43±2.81** | 61.15±2.75 | 60.42±2.2 | 55.36±2.0 | 55.46±2. | 51.86±2.78 |
| **10** | 58.44±1.77 | 68.15±2.62 | **78.67±3.77** | 76.15±3.4 | 71.74±2.9 | 76.15±3.1 | 74.46±3. | 67.76±3.56 |

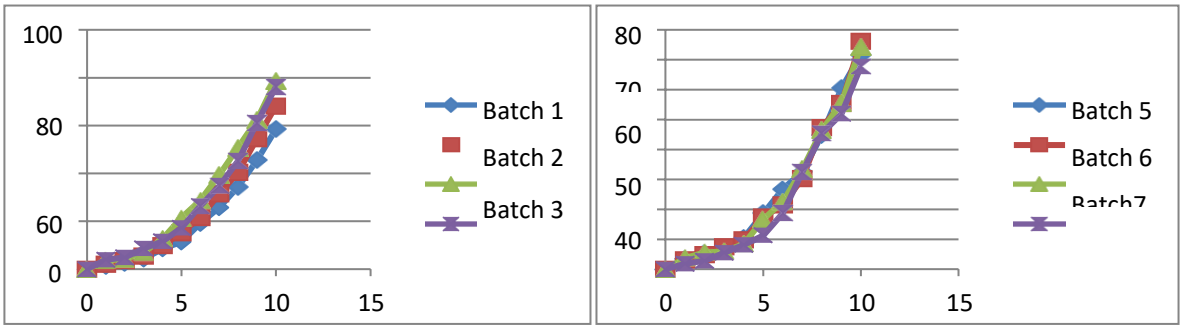



**Figure 9: In vitro skin permeation study**

**Release Kinetics Data Of Optimized Batch:**

**Table 8 : Release Kinetics Data Of Optimized Batch**

| **Release Kinetic Model** | **Regression Coefficient $(R)^2$** |
|---|---|
| Zero Order | 0.919 |
| First Order | 0.900 |
| Higuchi Model | 0.750 |
| Hixscon-Crowell Model | 0.912 |
| Koresmeyers- Papps Model | 0.754 |

**Evaluation Of Dpi :**

**Table 9 : .Evaluation Of Dpi**

| FORMULATION | Emitted dose(%) | MMAD (µm) | GSD (µm) | FP F (%) |
|---|---|---|---|---|
| BATCH 3 | 76.2 | 5.8 | 1.5 | 38.4 |

## CONCLUSION

It has been observed that microspheres are better choice of drug delivery system than many other types of drug delivery system because to it is having the advantage of target specificity and better patient compliance. It is concluded from above that microsphere is the promising candidate for sustained and as a targeted drug delivery in GIT, liver, colon, nasal, pulmonary system and ocular drug delivery etc. Its applications are vast as they are not only used for delivering drugs for particular disease but also for detecting and imaging tumours, detecting bio molecular interaction and used as diagnostic agent and

for treatment of cancer. Hence, in future microspheres will have an important role in the advancement of medicinal field.

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