# Incorporation of drug-resin complex to improve microsphere performance

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The objective of present work was to incorporate drug-resin complex (DRC) to microspheres to achieve improved drug loading, less leakage, and extended zero order release. Ondensetron hydrochloride (ODH), a model drug was complexed with Indion 244, and incorporated to microspheres of hydroxypropyl methyl cellulose (HPMC), and ethyl cellulose (EC). A $3^2$ full factorial design was used to prepare microspheres using HPMC and EC as independent variables, $X_1$ and $X_2$ respectively. The microspheres obtained were evaluated for yield, topology, micromeritics, drug entrapment, and drug release kinetics. Complexation of ODH with Indion 244 was found to be 28% wt/wt. The incorporation efficiency of DRC to microspheres (DRC1-DRC9) was in the range of 70.41 ± 2.18 to 95.08 ± 0.76% wt/wt. The trend of increase in the drug entrapment (DRC) with high amounts of HPMC and EC was noted for all microspheres. Yield of DRC9 was maximum (84.87% wt/wt), and was lowest for DRC1. Acceptable Hausner's ratio, Carr's compressibility index and angle of repose demonstrated the excellent flowability of microspheres (DRC1 to DRC9). Drug release kinetic studies showed that, ODH dissociation from DRC, and its diffusion through HPMC and EC, both, have contributed for extended zero order release. Especially, from DRC2, maximum extended release was noted up to 19.10 hrs (zero order, $R^2 = 0.9239$). Hence, it can be concluded that, incorporation of DRC to microspheres can overcome poor drug loading, high drug leakage, and poor drug sustainability problems of microspheres. Especially, the zero order release can be achieved by incorporation of DRC to microspheres.

Key words: Drug resin complex, extended zero order release, microspheres

## INTRODUCTION

Microspheres have been widely used in oral drug delivery due to their huge surface area, distribution throughout GI tract, reduced localised toxicity, and enhanced bioavailability.[1] However, the main constraints limiting its use include poor mechanical strength, poor drug loading, high drug leakage, and poor drug sustainability.[2] These problems become more prominent with water soluble drugs. To overcome these limitations, attempts have been made to cross link the polymers and application of polymer coat to microspheres. However, these methods also suffer from process complexity, poor drug loading, lack of reproducibility, etc.[3-5] Hence, to improve on these and extend the drug release, preferably zero order type, an attempt has been made to incorporate drug resin complex to the microspheres.

Present scenario of resin reveals its use as a taste masking agent, disintegrant, and release modifier in various dosage forms.[6] It has been observed that strong cation and anion exchange resins complexed with strong anionic and cationic drugs respectively extend the drug release for long time.[7,8]

In present study, attempt has been made to optimize the drug resin complexation process for model strong cationic drug, ondensetron hydrochloride and strong cation exchanger, Indion 244, and, this complex is then incorporated to microspheres prepared from hydroxypropyl methyl cellulose and ethyl cellulose. A $3^2$ full factorial design has been implemented to elucidate the effect of drug resin complex incorporation on yield, topology, micromeritics, drug entrapment, and drug release kinetics of microspheres.

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## Experimental materials

Ondensetron hydrochloride (ODH) was procured as a gift sample from Gouri Fine Chemicals, Pune, Maharashtra, India. Hydroxypropyl Methyl Cellulose (HPMC -15 cps) and Ethyl Cellulose (EC-7 cps) were gifted by Colorcon Asia Pvt. Ltd., Mumbai, Maharashtra, India. Indion 244 was a kind gift from Ion Exchange India., Mumbai, Maharashtra, India. Aerosil, Tween 80, and dichloromethane were purchased locally.

## Methods

### Fabrication of microspheres

#### Purification and activation of indion 244

Indion 244 was purified by using methanol to remove impurities.[9] The purified Indion 244 was washed with deionised water and filtered. Acid activation of resin was carried out by keeping Indion 244 in contact with 500 mL of 1 N HCl for 24 hrs with continuous stirring using magnetic stirrer. The suspension was filtered; separated resin (acid activated) was rewashed with deionised water several times till neutral pH and kept in desiccator to dry and for further use.[10]

### Optimization of drug resin complexation process

The batch process was adopted for complexation of ODH with Indion 244. Both the ODH, activated and dried Indion 244, were taken in various proportions viz: 1:1, 1:1.2, 1:1.4, 1:1.6, 1:1.8, 1:2, 1:2.2, 1:2.4, 1:2.8, 1:3.2, respectively, in 10 mL of deionised water separately. The slurry was allowed to equilibrate for 24 hrs with continuous stirring using magnetic stirrer. The slurred mass was filtered through Whatman grade No. 42 quantitative filter paper and the filtrate was analyzed spectrophotometrically at 310 nm for estimation of unbound drug. The difference in the amount of initial drug added and final amount of drug remaining in the solution was called as drug complexed/loaded. The values of slope (23.45) and y intercept (0.5893) obtained from standard curve were used for calculation of unbound drug.[11]

### Use of $3^2$ full factorial design

A $3^2$ full factorial design was used to prepare microspheres of EC, HPMC and drug resin complex (DRC). Amount of HPMC $(X_1)$ and amount of EC $(X_2)$ were considered as two independent variables. Nine batches of microspheres were prepared at three levels of X1 (-1, 0, +1; 0.33 g, 0.45 g, 0.6 g) and X2 (-1, 0, +1; 1.5 g, 2.25 g, 3 g). Table 1 gives the composition and total weight of microspheres.

In process, the homogenous powder mixture of DRC, EC, HPMC, aerosol, and Tween 80 was added to dichloromethane (DCM) in a 250 mL capacity beaker at room temperature. Subsequently, entire aqueous solution of PVP K-30 (100 mL) was poured to it with stirring. The contents were stirred using stirrer (Remi Motors, India) at 900 ± 50 rpm for 30 minutes. The microspheres obtained were filtered, washed with water and dried in oven at 40°C for 24 hrs.

A polynomial equation (equation 1) was generated to study the effect of independent variables on different evaluation responses *(Y)*.

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_{11} X_1{}^2 + \beta_{22} X_2{}^2 + \beta_{12} X_1 X_2 \qquad (1)$$

Where, $\beta_0$ is the arithmetic mean response of nine batches, $\beta_1$ coefficient of $X_1$, $\beta_2$ coefficient of factor $X_2$, $\beta_{12}$ the coefficient for interaction of $X_1$ and $X_2$, $\beta_{11}$ and $\beta_{22}$ coefficient of $(X_1)^2$ and $(X_2)^2$ respectively shows how dependant variable changes when two or more factors are simultaneously changed.[12]

### Evaluation of microspheres

#### Process yield

Yield of microspheres was determined for all nine batches (DRC1 to DRC9) separately in triplicate. The weight of dried microspheres $(W_1)$ of each batch, and initial powder weight (HPMC, EC, DRC, and Aerosil) $(W_2)$ was used to calculate process yield using the equation 2.[13,14]

$$\% \text{ yield} = (W1/W2) \times 100 \qquad (2)$$

### Surface topography

Randomly selected 10 microspheres from each batch were taken and subject to imaging and surface character studies. Photomicrographs of microspheres were taken using an optical microscope (Motic-DMB1, IMAGE 2000 software) at magnification 4× and 10×. Using Scanning Electron Microscopy (SEM) study (JEOL-JSM-6360A, Japan); the photomicrographs were taken at magnification of 120× and 1500× to observe the finer surface details of microspheres.[15,16]

### Measurement of flow properties

Flowability of microspheres was measured by angle of repose (θ) determined by fixed funnel free standing cone method.[17] All nine batches of microspheres were subject to θ determination in triplicate.

The values of CCI and the HR were calculated from the bulk density (BD) and tapped density (TD) obtained using bulk density apparatus (Lab Hosp, Mumbai, India).[18]

$$\text{Carr's Compressibility Index (CCI)} = [(TD\text{-}BD)/TD] \times 100 \qquad (3)$$

$$\text{Hausner's ratio (HR)} = TD/BD \qquad (4)$$

### Shape studies

Shape and sphericity of microspheres was determined from area and perimeter of microphotograph images taken using optical microscope having IMAGE 2000 software. Shape factor and circulatory factor were calculated using following equations.[19]

$$\text{Shape Factor (P)} = P''/P' \qquad (5)$$

**Table 1: Batch composition for microspheres: 3² factorial design\***

| Batch code | Composition | | | | | |
|---|---|---|---|---|---|---|
| | HPMC 15 cps g (levels) | EC-7 cps g (levels) | DRC (mg) | Aerosil (mg) | PVP-K30 (mg) | Total weight (g) |
| DRC1 | 0.30 (-1) | 1.5 (-1) | 304 | 54 | 10 | 2.168 |
| DRC2 | 0.60 (+1) | 3.0 (+1) | 304 | 54 | 10 | 3.968 |
| DRC3 | 0.30 (-1) | 3.0 (+1) | 304 | 54 | 10 | 3.668 |
| DRC4 | 0.60 (+1) | 1.5 (-1) | 304 | 54 | 10 | 2.468 |
| DRC5 | 0.30 (-1) | 2.25 (0) | 304 | 54 | 10 | 2.918 |
| DRC6 | 0.45 (0) | 1.5 (-1) | 304 | 54 | 10 | 2.318 |
| DRC7 | 0.60 (+1) | 2.25 (0) | 304 | 54 | 10 | 3.218 |
| DRC8 | 0.45 (0) | 3.0 (+1) | 304 | 54 | 10 | 3.818 |
| DRC9 | 0.45 (0) | 2.25 (0) | 304 | 54 | 10 | 3.068 |

*Each batch contained Tween 80, 5 mg; DCM, 10 ml and DW, 100 ml

Where $P'' = 2\prod (A/\prod)^{1/2}$

Circularity Factor $(S) = (P')^2 / (12.56 \times A)$     (6)

Where, P' was perimeter, and, A, area of microsphere.

### Drug entrapment studies

Exactly weighed 100 mg of microspheres equivalent to 4 mg of ODH were taken and triturated finely. To this, 100 mL of aqueous acid having pH 2.8 (0.2 M HCl) was added and sonicated for 15 minutes. Then, the dispersion was filtered through Whatman grade No. 42 quantitative filter paper and the absorbance of filtrate was taken at 310 nm in triplicate for all nine batches of microspheres and drug entrapment efficiency was calculated using following equation:[20]

Drug Entrapment efficiency = (Amount of actual drug present /Theoretical drug loading expected) × 100     (7)

### Drug release kinetics

Accurately weighed 100 mg of microspheres from each batch were weighed separately and subject to dissolution studies in triplicate in United States Pharmacopoeia type II dissolution test apparatus (TDT 08 L, Electrolab, Mumbai, India) in 900 mL of 0.1 N HCl maintained at $37 \pm 0.5°C$ and stirred by paddles at 100 rpm. Every time, 5 mL of sample was withdrawn and analyzed spectrophotometrically at 310 nm. Same amount of fresh 0.1 N HCl was used to replace the sample withdrawn and time required for complete drug release was noted.[21]

The data of % drug release and time was subject to PCP Disso V3 (Poona College of Pharmacy, Pune, Maharashtra, India) software for typing of drug release kinetics and identifying the best fit model.

## RESULTS AND DISCUSSION

### Fabrication of microspheres

Indion 244 is a strong cation exchange resin consisting of sulfonic acid functionality attached to an insoluble polystyrene divinylbenzene backbone, and ODH is a salt of strong base and strong acid, having pKa 7.4. In water, ODH generates strong cations, which can be exchanged with $H^+$ ion of Indion 244.[22] The complexation process is essentially a process of diffusion between resin functionalities and surrounding drug solution. In the swollen resin matrix, the coiled latent functionalities of resin backbone become uncoiled and get exposed to the surrounding medium leading to availability of exchange sites for ions in the surrounding medium.[23] It has been reported that cation exchange resin does not get significantly affected by temperature changes unlike anion exchangers.[24] Hence, in the present studies complexation process has been performed at ambient temperature without taking into consideration effect of temperature.

Reports state that complexation efficiency of batch process is higher than the column process.[25] The present complexation studies have showed 28% w/w loading/complexation of ODH to Indion 244. Although the extent of the drug complexation seems to be less, it is in agreement with the findings on loading efficiency of cimetidine on amberlite 69 (38.6% W/W). Pisal *et al.*, have demonstrated the similar findings for complexation efficiency of ciprofloxacin hydrochloride and Indion 234.[10] This poor complexation efficiency might have been seen due to higher degree of cross-linking of resin having tighter pore structure and smaller pore size preventing access of the drug molecule to the ionic site in the resin particle.[23]

### Evaluation of microspheres
#### Process yield

Yield of microspheres was found to be dependent on both amount of HPMC and EC, and was in the range of $48.35 \pm 3.03$ % w/w to $84.87 \pm 3.95$% w/w [Table 2]. From regression analysis [Table 3] it has been evident that, HPMC and EC, both, has affected the yield of microspheres ($\beta_1 = 8.3986$, $\beta_2 = 6.5233$). With the increase in concentration of HPMC, yield was increased to greater extent than EC. Statistically significant difference was observed between the yield values of all microsphere batches, DRC1-DRC9 at $P < 0.05$.[24]

## Surface topography

Figure 1 shows the optical microscopic and SEM images of microspheres. Figure 1a is of columnar crystals of pure ODH, which has been disappeared in the microspheres due to complexation with the Indion 244, as seen in Figure 1b. Distinct spots of brown colored DRC are seen incorporated to microspheres. The porous nature of microspheres is evident from SEM examination [Figure 1c]. The pores and cavities in the microspheres have been formed by rapid evaporation of the DCM during the process of microsphere formation.[25]

## Measurement of flow properties

Angle of repose is an indictor to assess the flowability of microspheres. Depending on the angle of repose ($\theta$), the categorization of microspheres can be carried out into good, bad, excellent, fair etc flow characters. Recently, Lalla *et al*, have studied the angle of repose for free flowing spheres and assigned $\theta$ in the range of 25-30° for excellent flowability.[26] In the present studies, $\theta$ was in the range of 20.29 ± 1.35° to 22.99 ± 0.32°, indicating fair flowability of microspheres. From nonlinear regression analysis [Table 3] it was evident that the overall effect of HPMC was reduction in $\theta$ ($\beta_1$ = -0.6808) with its increase in amount. The $\theta$ went on decreasing at medium level concentration of HPMC (450 mg)

and increased towards +1 and -1. But, reverse was true for EC ($\beta_2$ = 0.2667). It was maximum at intermediate '0' level, whereas least towards both extremes (-1 and +1). However, the overall effect of EC was increase in $\theta$, with increase in amount of EC. For all batches of microspheres, $\theta$ was in the range of 18.94 + 24.61, as given in Table 2.

Carr's compressibility index has been used to study the flowability and compressibility of the powder, granules, microspheres etc.[27] An ideal range of compressibility index for materials showing excellent flowability has been reported as 5 to 15 and it depends on tapped density and bulk density of solids. In the present study, majority of microsphere batches showed excellent flowability. The trend of decrease in CCI with increase in concentration of HPMC ($\beta_1$ = -0.1154), and increase in CCI, with increase in concentration of EC ($\beta_2$ = 0.1617) was in agreement with angle of repose studies [Table 2].

Similar to $\theta$ and CCI, Hausner's ratio has been used as a tool to assess the flowability. High HR value indicates extensive densification leading to more reduction in void volume.[28] Ideally, for excellent flowability of solids, the value of HR should be less than 1.25 and it was found in the range of 1.031 ± 0.06 - 1.090 ± 0.01. Similar to findings on $\theta$
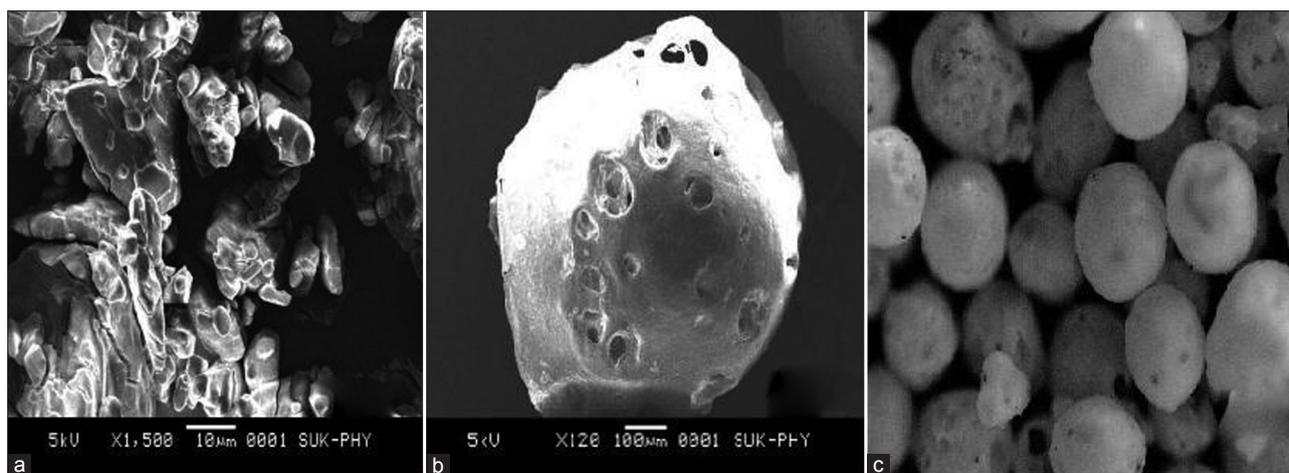


**Figure 1:** Scanning electron microscope (SEM) of pure drug ondensetron hydrochloride (ODH) (a), and floating microspheres containing drug-resin complex (DRC) (b), optical microscopic image of microspheres (c)

## Table 2: Values for yield, shape factors, and flowability parameters of microspheres

| Batch code | %Yield (wt/wt) | Circulatory factor | Roundness factor | Shape factor | Hausner's ratio | Carr's compressibility index | Angle of repose ($\theta$) |
|---|---|---|---|---|---|---|---|
| DRC1 | 48.35 ± 3.03 | 1.194 ± 0.062 | 1.00 ± 0.004 | 0.999 ± 0.11 | 1.085 ± 0.04 | 7.87 ± 0.88 | 21.45 ± 1.08 |
| DRC2 | 69.63 ± 4.46 | 1.056 ± 0.196 | 1.491 ± 0.337 | 0.586 ± 0.19 | 1.069 ± 0.01 | 6.52 ± 2.02 | 22.91 ± 1.7 |
| DRC3 | 50.65 ± 7.88 | 1.156 ± 0.314 | 1.342 ± 0.2197 | 0.762 ± 0.16 | 1.045 ± 0.05 | 4.34 ± 0.12 | 22.99 ± 0.32 |
| DRC4 | 58.87 ± 2.15 | 1.158 ± 0.102 | 1.213 ± 0.027 | 0.823 ± 0.01 | 1.063 ± 0.02 | 6.0 ± 1.30 | 20.86 ± 0.86 |
| DRC5 | 66.01 ± 17.84 | 1.359 ± 0.710 | 1.458 ± 0.205 | 0.718 ± 0.11 | 1.040 ± 0.01 | 4.25 ± 0.25 | 20.84 ± 1.04 |
| DRC6 | 73.52 ± 11.42 | 0.979 ± 0.124 | 1.323 ± 0.068 | 0.758 ± 0.06 | 1.470 ± 0.03 | 4.54 ± 0.28 | 20.39 ± 0.28 |
| DRC7 | 62.68 ± 5.84 | 1.029 ± 0.092 | 1.327 ± 0.0584 | 0.755 ± 0.05 | 1.045 ± 0.01 | 4.34 ± 0.12 | 20.29 ± 1.35 |
| DRC8 | 75.08 ± 6.69 | 1.050 ± 0.071 | 1.323 ± 0.064 | 0.757 ± 0.06 | 1.031 ± 0.06 | 4.87 ± 0.97 | 22.03 ± 2.31 |
| DRC9 | 84.87 ± 3.95 | 0.955 ± 0.130 | 1.317 ± 0.1048 | 0.761 ± 0.05 | 1.090 ± 0.01 | 8.33 ± 0.44 | 20.82 ± 0.44 |

**Table 3: Multiple regression analysis coefficients for response variables of microsphere batches (DRC1-DRC9)**

| Regression coefficients | Yield | Roundness | Circulatory factor | Shape factor | Carr's compressibility index | Hausner's ratio | Angle of repose ($\theta$) | Drug Entrapment (%) | t90% |
|---|---|---|---|---|---|---|---|---|---|
| $r^2$ | 0.808 | 0.899 | 0.521 | 0.748 | 0.947 | 0.953 | 0.823 | 0.994 | 0.907 |
| $\beta_1$ | 8.398 | 0.039 | -0.060 | 0.748 | -0.115 | -0.001 | -0.680 | 8.169 | 39.135 |
| $\beta_2$ | 6.523 | 0.073 | -0.048 | -0.049 | 0.161 | 0.001 | 0.266 | 4.905 | 45.566 |
| $\beta_{11}$ | -1.524 | -0.014 | -0.090 | -0.008 | 0.801 | 0.010 | 1.072 | 8.939 | 132.735 |
| $\beta_{22}$ | -5.880 | -0.205 | -0.080 | 0.146 | 1.302 | 0.021 | -0.835 | 0.786 | -67.710 |
| $\beta_{12}$ | 3.608 | -0.104 | -0.010 | 0.073 | 1.852 | 0.016 | -0.125 | 0.203 | -12.332 |

and CCI, the values of HR were found to be maximum for microspheres containing least amount of HPMC and EC. With increase in amount of HPMC the value of HR was found to be decreased ($\beta_1$ = -0.0015) and got increased with increase in concentration of EC ($\beta_2$ = 0.0018).

*Shape studies*

Sphericity and shape determination are essential parameters for measurement of flowability and packability of microspheres. Values of sphericity and shape parameters have been given in Table 2, whereas their regression coefficients are given in Table 3.

Roundness

Roundness is a parameter used to define the shape of the particles. The roundness of all batches

(DRC1-DRC9) was in the range of 1000 ± 0.0004 to 1.491 ± 0.3372. It was seen that at medium level of EC, '0', roundness was maximum, which decreased with the extremes of the EC content. In case of HPMC, with increase in its amount roundness decreased.[25]

Circularity factor

Similar to roundness factor, circulatory factor has been considered for defining shape of the particles. It was observed that HPMC and EC contribute towards decrease in circulatory factor, which has been clearly evident from regression analysis coefficients, $\beta_1$, -0.0600; $\beta_2$, -0.0487.

Shape factor

The shape factor values for microspheres were ranging from 0.586 ± 0.19 to 0.999 ± 0.11. The response surface studies showed that at extreme levels of EC, improvement in shape factor has been noted and it was maximum at lowest levels of HPMC and EC [Figure 2], thus trend of reduction in shape factor values with increase in concentration of HPMC was noted.

*Drug entrapment and loading*

During the preparation of microspheres, an addition of EC, HPMC, DRC, aerosil, and Tween to DCM generated viscous mass. However, its dispersion to external aqueous phase was assisted by addition of Tween 80 and PVP–K30 acting as an emulsifying/distributing agent. This resulted in to generation of globules having DRC incorporated to it. Due

**Table 4: % Drug entrapment and drug release kinetics data for microspheres**

| Batch code | % Drug entrapment (%w/w) | $t_{90\%}$ (hrs) | $R^2$ | Best fit model |
|---|---|---|---|---|
| DRC1 | 70.41 ± 2.18 | 09.27 | 0.9293 | Zero order |
| DRC 2 | 72.99 ± 0.07 | 19.10 | 0.9239 | Zero order |
| DRC 3 | 79.02 ± 0.13 | 16.62 | 0.9589 | Zero order |
| DRC 4 | 72.62 ± 0.11 | 10.39 | 0.9198 | Zero order |
| DRC 5 | 73.10 ± 0.27 | 15.48 | 0.9566 | Zero order |
| DRC 6 | 79.39 ± 0.17 | 10.71 | 0.9531 | Zero order |
| DRC 7 | 86.03 ± 1.15 | 16.22 | 0.9587 | Zero order |
| DRC 8 | 90.53 ± 0.64 | 17.03 | 0.9634 | Zero order |
| DRC 9 | 95.08 ± 0.76 | 16.76 | 0.9622 | Zero order |

to the stirring carried out to aid the emulsification hastened the evaporation of DCM from microspheres leaving behind holes at the surface, and has been confirmed form SEM image. The amount of ODH entrapped in the microspheres was confirmed as 67.62 ± 0.11 to 95.08 ± 0.76 w/w, indicating satisfactory DRC entrapment [Table 4]. Figure 3 (response surface graph) shows that batch DRC9 having intermediate levels of HPMC and EC had maximum drug entrapment (95.08 ± 0.76 % w/w). However, similar studies carried out on cimetidine microspheres prepared from HPMC and EC, has shown drug entrapment in the range of 52.1 ± 2.3 to 63.5 ± 5.2 w/w,[16] and is quiet less than the ODH entrapment in present studies. Improved drug entrapment can be attributed to incorporation of drug in the form of DRC, i.e., DRC in its fine particulate form, gets incorporated to microspheres overcoming all constraints related with the drug loading efficiency.

*Drug release kinetics*

Literature reveals that, microspheres do not extend the drug release for longer time. The release of cimetidine from microspheres of HPMC and EC could extend up to 8 hours showing Higuchi matrix model.[16] It indicated the release of drug controlled by diffusional path length and ultimately the gel of HPMC formed in the microspheres shell structure. But, present studies have demonstrated that ODH release rate was dependant on its dissociation from Indion 244 followed by diffusion through the microspheres shell. Consequently, ODH release followed zero order kinetics in all batches of microspheres, irrespective of levels of HPMC and EC controlling the release of drug [Table 4, Figures 4 and 5].
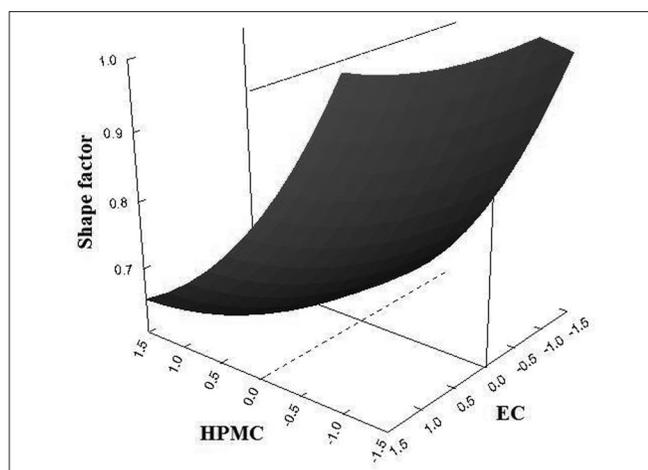
**Figure 2:** Response surface plot showing effect of hydroxypropyl methyl cellulose (HPMC) and ethyl cellulose (EC) on shape factor
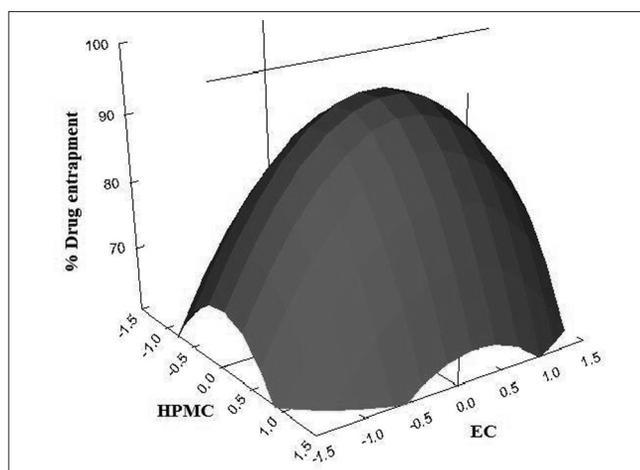


**Figure 3:** Response surface plot showing effect of hydroxypropyl methyl cellulose (HPMC) and ethyl cellulose (EC) on % drug entrapment
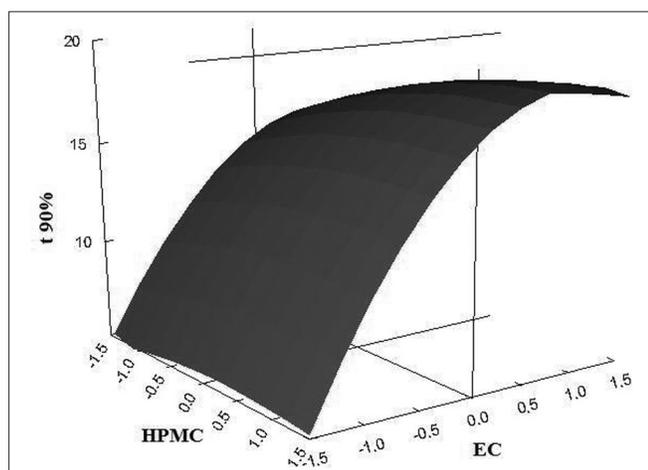


**Figure 4:** Response surface plot showing effect of hydroxypropyl methyl cellulose (HPMC) and ethyl cellulose (EC) on $t_{90}$%



**Figure 5:** Drug release profile for DRC1 to DRC9 batches

Hence, to achieve zero order drug release, the present concept can be easily adopted. The drug release retardant effect of HPMC and EC was clearly seen in DRC2 ($t_{90\%}$ = 19.10 hrs, $r^2$ = 0.9293), at higher levels (+1, +1), and at lowest concentration (-1, -1), release was extended for shorter time. This has clearly indicated that in addition to the rate of dissociation of ODH from DRC, amount of HPMC and EC, both play an important role in extension of drug release. Although regression analysis demonstrates the predominant effect of EC on release ($\beta_2$ = 45.566) than HPMC ($\beta_1$ = 39.135). The swollen layer of HPMC and erodible layer of EC, both, control the release of ODH release.

## CONCLUSION

Incorporation of drug-resin complex to microspheres was satisfactory and the improvement in drug incorporation efficiency to microspheres was attributed to complexation of ODH with Indion 244. Especially, for incorporation of water solubl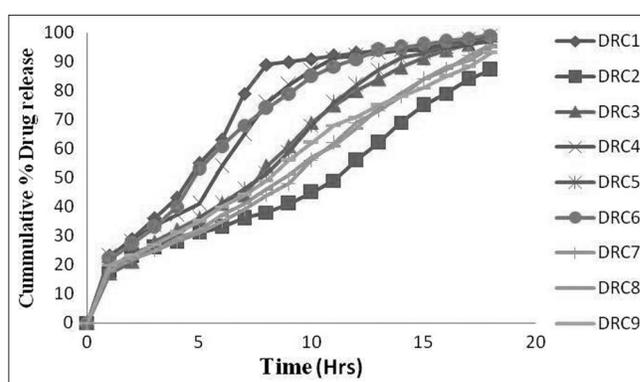e drugs, the technique holds promise to improve drug loading, reduce leaching and achieve extended release. Moreover, the release of drug from the microspheres can be modelled to zero order type by incorporating drug resin complex to it.

## ACKNOWLEDGEMENTS

## REFERENCES

1.  Neau SH, Chow MY, Durrani MJ. Fabrication and characterization of extruded and spheronized beads containing carbopol 974P, NF resin. Int J Pharm 1996;131:47-55.
2.  Malay S, Namdeo J, Yadvendra K. Carbon nanotube as adsorbent for floating microspheres of diltiazem hydrochloride. Fullerenes Nanotubes and Carbon Nanostructures 2009;17:528-47.
3.  Choi JS, Han HK. Enhanced oral exposure of diltiazem by the concomitant use of naringin in rats. Int J Pharm 2005;305:122-8.
4.  Ito F, Fujimori H, Makino K. Factors affecting the loading efficiency of water-soluble drugs in PLGA microspheres. Colloids Surf B Biointerfaces 2008;61:25-9.
5.  McGinity JW, O'Donnell PB, Preparation of microspheres by the solvent evaporation technique. Adv Drug Deliv Rev 1997;28:25-42.

6.  Jadhav NR, Shinde MV, Bhakare HR, Bhatia NM. Therapeutic applications of ion exchange resins: An update. Available from: http://www.Pharamainfo.net 2007. [Last accessed on 2010 Feb 9].
7.  Bhalekar M, Avari JG, Jaiswal SB. Cation-exchanger in pharmaceutical formulation. Indian J Pharm Sci 2004;38:184-7.
8.  Sriwongjanya M, Bodmeier R. Effect of ion exchange resins on the drug release from matrix tablets. Eur J Pharm Biopharm 1998;46:321-7.
9.  Pisal S, Zainnubuddin R, Nalawde P, Mahadik K, Kadam S. Molecular properties of ciprofloxacin-Indion 234 complexes. AAPS PharmSciTech 2004;5:e62.
10. Pisal S, Nalawde P, Mahadik K, Kadam S. Drug release properties of polyethylene-glycol-treated ciprofloxacin- Indion 234 complexes. AAPS PharmSciTech 2004;5:e64.
11. Arion NM. Process for the regeneration of Ion exchange resin and application thereof; United States patent 3,956,115. 1976.
12. Bolton S. Pharmaceutical Statistics 2. New York, NY: Marcel Decker Inc; 1990. p. 234.
13. Patel J, Kale R. Bioadhesive microspheres and their pharmaceutical applications. Drug Deliv Tech 2007;7: 54-60.
14. Patel A, Ray S, Thakur R. *In vitro* evaluation and optimization of controlled release floating drug delivery system of metformin hydrochloride. DARU J Pharm Sci 2006;14:57-64.
15. Nepal PR, Chun MK, Choi HK. Preparation of floating microspheres for fish farming. Int J Pharm 2007;341:85-90.
16. Shrivastsv A, Wadhwa S, Ridhurkar D. Floating microspheres of cimetidine: formulation characterization and *in vitro* evaluation. Acta Pharm 2005;55:277-85.
17. Jai SK. Agrawal GP, Jain NK. Evaluation of porous carrier-based floating orlistat microspheres for gastric delivery. AAPS PharmSciTech 2006;7:90.
18. Jadhav NR, Bhelkar KK, Bhakre HR, Garala KC, Gaikwad VL. Studies on unusual compression behaviour of paracetamol in presence of sodium chloride, gelatin and starch. Current Pharma Research J 2007;01:31-5.
19. Jadhav N, Pawar A, Paradkar A. Design and evaluation of deformable talc agglomerates prepared by crystallo-co-agglomeration technique for generating heterogeneous matrix. AAPS PharmSciTech 2007;8:E59.
20. Joseph NJ, Laxmi S, Jayakrishnan A. A floating-type oral dosage from for piroxicam based on hollow microspheres: *in vitro* and *in vivo* evaluation in rabbits. J Control Release 2002;79:71-9.
21. Janyaprasert VB, Manwiwattanakul G. Release profile comparison and stability of diltiazem-resin microcapsules in sustained release suspensions. Int J Pharm 2008;352:81-91.
22. Jain NK. Advanced drug delivery system. 1. Vol. 1. Delhi, India: CBS Publishers and Distributors; 2005. p. 290-302.
23. Christ AG, Process for the conditioning of ion exchange resins. United States patent 5,443,740. 1995. p. 15-58.
24. Spinger B. Synthetic ion exchange resins. Vol. 70/1985. Heidelberg: Spingerlink; 2006. p. 71-118.
25. Dale, James A, Lorenzo M, Lawrence S. Macroporous resins having large pores but with high crush strength. United States patent 6,323 249. Nov 27, 2001.
26. Lalla JK, Bhat SU. A look at process costing and cost effectiveness of a pharmaceutical formulation. Indian Drugs 1995;32:551-60
27. Carr RL. Evaluating flow properties of solids. Chem Eng 1965;72:163-8.
28. Hausner HH. Friction conditions in a mass of metal powder. Int J Powder Metall 1967;3:7-13.