

## Porous nanoparticles of metoprolol tartrate produced by spray-drying: Development, characterization and *in vitro* evaluation

MOHAMMED S. KHAN\*  
GOWDA D. VISHAKANTE  
H. G. SHIVAKUMAR

*Department of Pharmaceutics  
JSS College of Pharmacy, JSS University  
Sri Shivarathreeshwara Nagara  
Mysore-570015, India*

The present investigation was undertaken to fabricate porous nanoparticles of metoprolol tartrate by spray-drying using ammonium carbonate as pore former. Prepared nanoparticles were coated with Eudragit S100 polymer in order to prevent the release of metoprolol tartrate in the upper GI tract. It was shown that nanoparticles with low size ranges can be obtained with a low feed inlet rate. Micromeritic studies confirmed that nanoparticle batches are discrete and free flowing. Effects of the pore former on drug loading, porosity and *in vitro* release were studied. It was found that there was an increase in drug loading and porosity with increasing the amount of pore former. *In vitro* drug release studies showed that an increase in pore former made drug release faster. Release kinetics proved that nanoparticles follow a zero-order release mechanism.

**Keywords:** metoprolol tartrate, porous nanoparticles, spray-drying, gel permeation chromatography

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Oral route has been the most popular route for sustained delivery of drugs because of its convenience and ease of administration, greater flexibility in dosage form design. Controlled release delivery systems provide a uniform concentration or amount of drug at the absorption site and thus, after absorption, allow maintenance of plasma concentration within a therapeutic range, which minimizes side effects and also reduces administration frequency. Chitosan is a linear hydrophilic polysaccharide polymer of D-glucosamine. Chitosan in the form of nanoparticulate systems has been already reported as a promising carrier for the delivery of peptides, proteins, oligonucleotides and plasmids (1–3).

Spray-drying is a technique that allows instantaneous drying of solutions, suspensions or emulsions. It has been widely used in making nanoparticulate drug delivery systems (4–6).

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\* Correspondence; e-mail: [mshuaibkhan68@gmail.com](mailto:mshuaibkhan68@gmail.com)

The presence of pores in ceramic foams offers the possibility of using these porous ceramics as carriers for local and controlled delivery of drugs. Ammonium carbonate (AC) has been already used as a pore former to produce porous microparticles of bendorfumethazide by spray-drying (7). Metoprolol tartrate (MT) is a  $\beta$ -selective adrenergic blocking agent and is prescribed widely in cardiovascular diseases such as hypertension, angina pectoris, arrhythmias and myocardial infarctions.

In the present study, spray-dried porous nanoparticles (NP) of metoprolol tartrate (MT) were prepared using ammonium carbonate (AC) as pore former in order to maintain a constant plasma concentration within the desired period and ensure the desired therapeutic response. Various factors, including the effect of inlet rate on particle size, effect of pore former on the porosity of prepared nanoparticulate batches and the effect on drug release, were investigated.

## EXPERIMENTAL

### *Materials*

Metoprolol tartrate was obtained as a gift sample from AstraZeneca Pvt. Ltd., India. Chitosan was procured from Sigma Aldrich, India. Ammonium carbonate and directly compressible microcrystalline cellulose (MCC) were procured from Loba Chemie Pvt. Ltd., India. Eudragit S100 was received as a gift sample from Evonik Degussa Pvt. Ltd., India. Other reagents were of analytical grade.

### *Preparation of spray-dried porous nanoparticles*

Chitosan solution in aqueous acetic acid was prepared under continuous magnetic stirring. To the prepared chitosan solution, ammonium carbonate (pore former) was added under stirring to get the final spray-drying solution. Polyvinyl alcohol (PVA), in varying concentrations, had been added to the spray-drying solution as an emulsion stabilizer. Prepared solution was spray-dried with a Büchi 290 spray-dryer (Büchi, Switzerland) operating in the closed mode, using the Büchi 295 inert loop and nitrogen as the drying gas under standard operating conditions (7). Each formulation was prepared in triplicate (Table I).

### *Drug loading of metoprolol tartrate in porous NP batches*

Loading of MT was done through incubating NP batches in a 3 % (*m/V*) drug solution under mild agitation at room temperature. The loading capacity of uncoated particles was calculated in an indirect way, quantifying the amount of MT that remained in solution.

### *Coating of porous nanoparticles*

Enteric coating of all NP formulations bearing MT was done by spray coating in a conventional coating pan (8). In brief, the coating solution was prepared by mixing Eu-

Table I. Formulation chart of prepared NP formulations.

| Formulation code | Chitosan/ammonium carbonate mass ratio | Acetic acid (% <i>m/V</i> ) | PVA (% <i>m/V</i> ) |
|------------------|--|-----------------------------|---------------------|
| CH1              | 1: 0.15                                | 2                           | 1                   |
| CH2              | 1: 0.45                                | 2                           | 1                   |
| CH3              | 1: 0.75                                | 2                           | 1                   |
| CH4              | 1: 0.15                                | 2                           | 2                   |
| CH5              | 1.5: 0.45                              | 2                           | 2                   |
| CH6              | 1.5: 0.75                              | 2                           | 2                   |
| CH7              | 2: 0.15                                | 2                           | 4                   |
| CH8              | 2: 0.45                                | 2                           | 4                   |
| CH9              | 2: 0.75                                | 2                           | 4                   |

PVA – polyvinyl alcohol

dragit S100 with acetone for 1 h using a stirrer. After an hour, triethyl citrate (TEC) 2 % was added and stirring was continued for 30 min. The NPs were coated in a conventional pan at 20 rpm, at a coating solution spray rate of 2 mL min<sup>-1</sup> and inlet temperature of 60 °C. Coating of NP batches was continued till the mass gain was 2 % per average mass of the NP in the pan. The coated NP batches were dried in an oven at 35 °C for one day and stored in an air-tight container.

#### *Micromeritic properties*

Both poured (or fluff) bulk (Do) and tapped bulk densities (DF) were determined with a 10-mL graduated cylinder using a bulk density apparatus. Angle of repose was calculated by the fixed funnel method and *in vitro* porosity was computed and was expressed in percentage (9).

#### *Drug content*

For drug content uniformity NPs (100 mg) were crushed and then transferred into a 250-mL volumetric flask. The volume was adjusted with pH 7.4 phosphate buffer and kept on a rotary shaker for 24 h in order to completely extract the drug. The mixture was filtered, and the drug was assayed spectrophotometrically at 222 nm using a Shimadzu UV-1800 instrument (Japan).

#### *Particle size and zeta potential of prepared nanoparticles*

Size and zeta potential of MT loaded NPs were measured by photon correlation spectroscopy (PCS) using a Zetasizer Nano ZS (Malvern Instruments, UK). The particle size analysis was performed at a scattering angle of 90 °C at room temperature. Concentration of the particles was adjusted to an appropriate value by pure water filtered through a 0.22- $\mu$ m membrane. The diameter was averaged from three parallel measurements and expressed as mean  $\pm$  standard deviation.

### *Fourier transform infrared radiation measurements (FTIR)*

FTIR analysis was carried out for pure drug and for the formulation using the KBr pellet method on a FTIR spectrophotometer type Shimadzu model 8033 in order to ascertain compatibility between the drug and polymer used.

### *Gel permeation chromatography*

Molecular mass measurements were carried out using size exclusion chromatography (GPC) (pump Waters model 501, injector Waters model U6K, USA). Commercially available Bio-Gel TSK columns (ToyoSoda, Japan) were used. A Knauer HPLC pump Type 64.00 and Rheodyne injector were used, with a refractive index detector Model ERC 7512 (Erma CR., Inc., Japan).

### *Differential scanning calorimetry (DSC)*

All dynamic DSC studies were carried out on a DuPont 900 differential thermal analyzer (USA). The instrument was calibrated using high purity indium metal as standard. Dynamic scans were taken in a nitrogen atmosphere at the heating rate of 10 °C min<sup>-1</sup>.

### *Scanning electron microscopy (SEM)*

SEM photographs were taken with a scanning electron microscope Model Jeol, Japan, LV-5600, at the required magnification at room temperature. The photographs were studied to visualize the porous structure of the MT loaded NPs.

### *Transmission electron microscopic study (TEM)*

TEM was used to observe the morphology of MT loaded NPs. Sample was first diluted and a drop was placed onto a carbon coated copper grid and dried in an oven at 40 °C for 15 min. The images were taken using a Hitachi, Japan Ultra-thin film evaluation system (HD-2300A) in phase contrast, Z contrast, secondary electron modes.

### *X-ray powder diffraction (XRPD)*

X-ray powder diffraction patterns were recorded at room temperature with a D8 Advance wide-angle diffractometer (Bruker AXS, Germany) in the range of 5–40° of 2θ. Tablets for XRPD analysis were made with KBr and analyzed with an IR Perkin-Elmer model 1420, in the range from 4000 to 600 cm<sup>-1</sup>.

### *In vitro drug release studies and validation of UV-spectroscopic method*

*In vitro* drug release studies were performed using a USP (10) dissolution rate apparatus (apparatus 1, 100 rpm, 37 ± 0.5 °C) in pH 1.2 hydrochloric acid buffer (900 mL) for 2 h as the average gastric emptying time. Then, the dissolution medium was replaced with a pH 7.4 phosphate buffer (900 mL) for the rest of the dissolution studies till complete drug release was obtained. MT loaded NPs equivalent to 50 mg of drug were placed into a dialysis bag (cut-off 50,000 Da). The amount of MT released from the NPs at different

time intervals was determined spectrophotometrically at 222 nm. All experiments were done in triplicate.

Validation of the analytical method for MT quantification was performed according to the method adopted by Baloğlu and Şenyiğit (11) with slight modifications. Specificity tests finally proved that there was no interference between the polymers and MT. Results show a relative standard deviation (RSD) less than 0.5 and 1.3 % indicating good repeatability and reproducibility, respectively.

### *Release kinetics and mechanism*

In order to analyze the drug release mechanism, *in vitro* release data were fitted into various drug release models such as zero-order, first order, Higuchi, Hixon-Crowell cube root law and Korsmeyer-Peppas model (12–14).

## RESULTS AND DISCUSSION

### *Effect of feed inlet rate on nanoparticle size*

In the spray-drying process, the function of the peristaltic pump is to carry the polymer solution to the nozzle. This parameter could considerably influence the efficacy of the drying process (15). To see the effect, formulation batches were spray dried at different feed inlet rates (0.5, 3 and 6 mL min<sup>-1</sup>) so as to see the effect of the inlet feed rate on particle size. It was clearly observed that low pump values yielded the best results with regard to nanoparticulate morphology (data not shown). Use of the 0.5 mL min<sup>-1</sup> inlet rate led to formation of discrete spherical particles characterized by a smooth surface.

This may be attributed to the fact that during the spray-drying process, high pump rates result in a large volume of spraying solution to be dried, but heated air might not transform liquid droplets into solid droplets immediately leading to the formation of bigger irregular-shape particles that are not completely dried and tend to form aggregates (16, 17).

In short, the pump inlet rate influences the particle size and morphology. Thus, to keep the particle size within a small range, the inlet feed pump rate should be kept low because an increase in flow leads to an increase in the mean diameter of particles from 0.368 nm (at 0.5 mL min<sup>-1</sup>) to 4.89 nm (at 6 mL min<sup>-1</sup>).

### *Micromeritic properties*

Micromeritic properties for prepared nanoparticles are shown in Table II. It was found that the presence of a pore former affects the nanoparticle density and % porosity. For CH1 to CH9 formulations bulk density varies from  $0.287 \pm 0.027$  to  $0.219 \pm 0.017$ , tap density from  $0.83 \pm 0.02$  to  $0.57 \pm 0.26$  and porosity from 63.1 to 79.2 %. Angle of repose shows a good flowing property of prepared batches of nanoparticles. Due to the presence of the pore forming agent, there was variation in the density parameter; density of the formulation decreased (CH1 to CH3) and porosity of the nanoparticles batches increased with increased concentration of the pore forming agent. The same phenomenon was observed for other batches.

Table II. Micromeritic properties of different batches of NP prepared.

| Formulation code | Bulk density (g cm <sup>-3</sup> ) | Tap density (g cm <sup>-3</sup> ) | Angle of repose | Porosity (%) |
|------------------|------------------------------------|-----------------------------------|-----------------|--------------|
| CH1              | 0.287 ± 0.027                      | 0.83 ± 0.02                       | 23.13 ± 1.86    | 63           |
| CH2              | 0.261 ± 0.046                      | 0.77 ± 0.04                       | 22.16 ± 2.56    | 67.9         |
| CH3              | 0.233 ± 0.016                      | 0.70 ± 0.16                       | 22.29 ± 1.37    | 73.3         |
| CH4              | 0.293 ± 0.026                      | 0.71 ± 0.23                       | 26.18 ± 1.81    | 64.6         |
| CH5              | 0.271 ± 0.062                      | 0.69 ± 0.11                       | 23.31 ± 1.53    | 71.7         |
| CH6              | 0.254 ± 0.087                      | 0.65 ± 0.19                       | 24.21 ± 2.76    | 78.3         |
| CH7              | 0.295 ± 0.061                      | 0.75 ± 0.22                       | 21.20 ± 2.16    | 65.2         |
| CH8              | 0.256 ± 0.049                      | 0.63 ± 0.17                       | 26.17 ± 2.06    | 72.3         |
| CH9              | 0.219 ± 0.017                      | 0.57 ± 0.26                       | 27.23 ± 1.17    | 79.2         |

Mean ± SD, *n* = 3.

### Effect of pore former on drug loading

There was a considerable effect of the pore forming agent on drug loading efficiency of prepared nanoparticle batches. In case of CH1 to CH3, drug loading varied between 42.3 ± 1.7 and 74.7 ± 1.6 %. Drug loading increased as the concentration of the pore forming agent increased. The same observation applies to other batches. For CH4 to CH6 drug loading varies between 44.7 ± 1.1 and 77.3 ± 1.1 % and for CH6 to CH9 between 51.3 ± 1.2 and 81.3 ± 1.4 %. There was a slight increase in drug loading efficiency for CH6 to CH9 compared to other batches. This may be attributed to the fact that higher concentration of chitosan present here holds a higher amount of drug within its matrix.

### FTIR and DSC

Nanoparticulate batches CH7 to CH9 were taken into consideration as suitable formulations because of their small size, high zeta potential compared to other formulated batches and ability to prolong the drug release rate for a particular period of time. Among them, formulation CH8 was randomly chosen for DSC and FTIR studies.

The DSC thermogram for pure drug showed a sharp endotherm at 122.9 °C, which corresponds to its melting. Thermogram of the formulation showed the endotherm at 121.9 °C, as shown in Fig. 1a. Physical mixture showed a broadened peak at the same temperature. This reveals that there was no interaction between the drug and excipients used.

Metoprolol tartrate exhibited a broad band at 3440.77 cm<sup>-1</sup> for aliphatic C-H stretch. In case of the formulation, a peak occurs at 3438.37 cm<sup>-1</sup> for aliphatic C-H stretch. Physical mixture showed a peak value of 3439.33 cm<sup>-1</sup> corresponding to the C-H stretch, as shown in Fig. 1b, thus ruling out any interactions between the drug, polymer and excipients used.

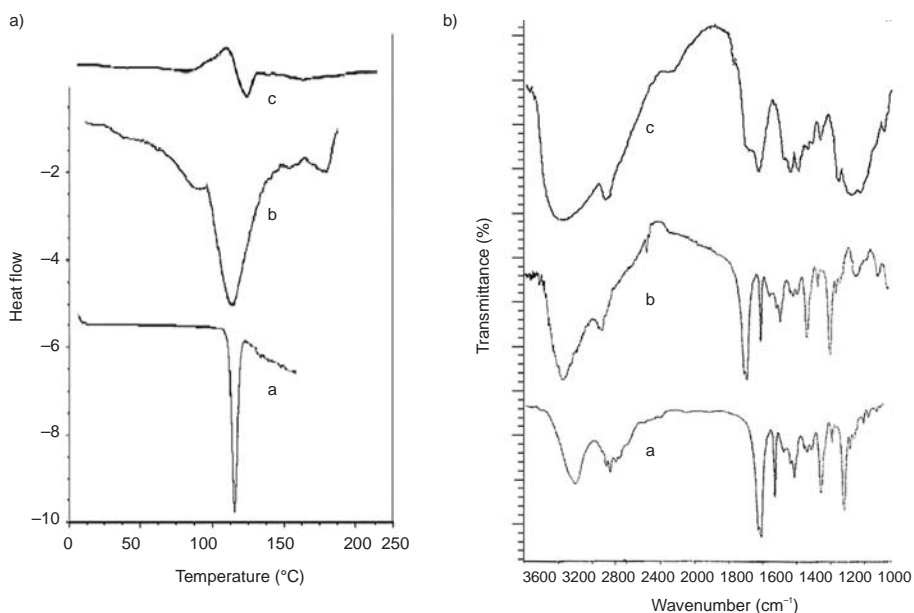


Fig. 1. a) DSC and b) FTIR spectra of: pure drug (a), formulation CH8 (b) and physical mixture (c) of metoprolol tartrate, chitosan, ammonium carbonate and Eudragit S100.

### SEM, TEM and zeta potential

Nanoparticle surface morphology and shape were investigated using SEM and TEM analyses. SEM images completely revealed that the drug loaded nanoparticles were distinct, spherical, having a porous surface (Fig. 2a).

However, in case of nanoparticulate batches having higher concentration of the pore forming agent, the surface of nanoparticles was found to be rough because of the large amount of pores formed due to the leaching out of ammonium carbonate from the matrix of nanoparticles during the vaporized process (18).

TEM analysis (Fig. 2b) is in conformity with SEM analysis, showing the spherical shape of prepared nanoparticles with homogeneous drug distribution within the nanoparticles prepared. Since from SEM and TEM analyses it was clearly seen that there was no surface drug present on nanoparticles or there was no accumulation of drug particles on the surface or within its matrix, so it can be said that the drug is homogeneously distributed in nanoparticles.

Zeta potential was found to be in the range from  $-11.9 \pm 0.8$  to  $-21.3 \pm 1.7$  for CH1 to CH9 formulations. In general, particle aggregation is less likely to occur for charged particles (high zeta potential) due to electric repulsion. Lower zeta potential facilitates aggregation of nanoparticles. Strong negative charge may provide a basis for the overall high stability of the nanoparticulate suspension.

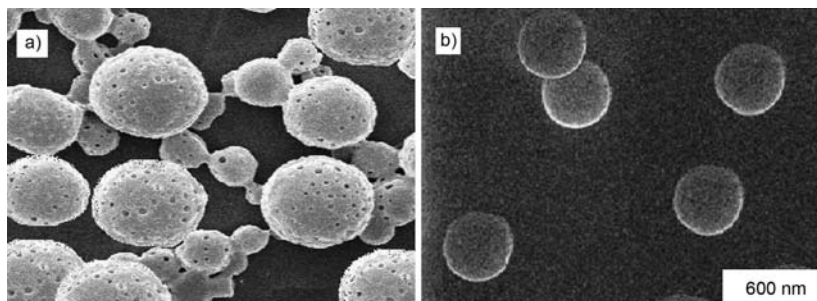


Fig. 2. a) SEM and b) TEM analysis of CH8 formulation.

### Size distribution

Average size of prepared nanoparticles varied between  $687.0 \pm 1.3$  and  $317.0 \pm 2.1$  nm with a polydispersity index ranging from  $0.767 \pm 0.003$  to  $0.354 \pm 0.034$  (Table III). Zeta potential for all nanoparticle formulations was found to be high indicating stability of nanoparticles.

### X-ray powder diffraction

Fig. 3 shows the XRPD pattern of pure MT and of nanoparticles prepared by the spray-drying method. XRPD of pure MT show distinctive peaks that indicate high crystallinity of MT. MT peaks are hardly observed in the formulation diffractogram. Disappearance of crystalline peaks of the drug in the prepared nanoparticulate batches indicates an amorphous state of the drug in the spray-dried formulations.

Table III. Evaluated particle size results of spray dried nanoparticles

| Formulation code | Polydispersity index | Average size (nm) | Zeta potential (mV) |
|------------------|----------------------|-------------------|---------------------|
| CH1              | $0.767 \pm 0.003$    | $687 \pm 1.3$     | $-11.9 \pm 0.8$     |
| CH2              | $0.717 \pm 0.013$    | $673 \pm 0.3$     | $-12.6 \pm 1.2$     |
| CH3              | $0.759 \pm 0.022$    | $654 \pm 1.7$     | $-12.3 \pm 1.5$     |
| CH4              | $0.747 \pm 0.011$    | $584 \pm 2.5$     | $-13.8 \pm 2.3$     |
| CH5              | $0.713 \pm 0.035$    | $571 \pm 1.7$     | $-14.1 \pm 0.7$     |
| CH6              | $0.653 \pm 0.021$    | $554 \pm 0.8$     | $-13.7 \pm 1.8$     |
| CH7              | $0.378 \pm 0.091$    | $321 \pm 1.4$     | $-21.3 \pm 1.6$     |
| CH8              | $0.398 \pm 0.027$    | $343 \pm 1.1$     | $-21.2 \pm 2.1$     |
| CH9              | $0.354 \pm 0.034$    | $317 \pm 2.1$     | $-21.3 \pm 1.7$     |



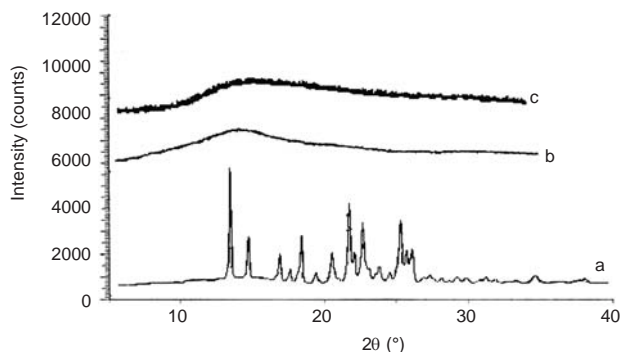


Fig. 3. XRPD diffraction patterns of: a) pure drug, b) formulation CH8, c) physical mixture of metoprolol tartrate, chitosan, ammonium carbonate and Eudragit S100.

### *Gel permeation chromatography*

Gel permeation chromatography analysis was carried out in order to establish and verify if the conditions employed during the spray-drying process caused any chitosan degradation. Data obtained after GPC analysis showed that no/negligible change in polymer molecular mass occurred after spray-drying of chitosan. Molecular mass of chitosan was 5,000 before spray-drying and it was found to be the same after spray-drying. The average molecular mass and polydispersity index of the polymer before the spray-drying process, as well as those of the polymer after spray-drying and of the polymer with drug, were determined and no changes were found.

### *Effects of pore forming agent and polymer concentration on drug release*

Drug release of all prepared porous nanoparticulate batches is shown in Fig. 4. It is clearly shown that from all batches of porous nanoparticles, no drug release took place in the first 2 h at pH 1.2 because of the enteric coating by Eudragit S100. This shows that enteric coating by Eudragit S100 (2%, *m/V*) efficiently prevents drug release from porous NPs at gastric pH 1.2. Drug release started after changing the dissolution media pH to 7.4. Dissolution of the enteric coat brings the porous nanoparticle surface in direct contact with the dissolution media. Drug was released in a controlled manner due to the hydration ability of chitosan, which on coming in contact with media leads to the formation of a gelatinous mass that acts as retardant material for the drug to diffuse out.

Effect of the pore forming agent was investigated so as to see the impact of pores formed that will affect the drug release. In case of formulations CH1 to CH3, drug release was found to be rapid. It was observed that within a period of 8 h maximum drug was released by nanoparticles CH1 ( $95.2 \pm 1.3\%$ ), CH2 ( $99.8 \pm 1.3\%$ ) and CH3 ( $98.9 \pm 1.3\%$ ). However, release took place in a linear fashion. CH1 and CH2 released maximum amount of the drug in 8 h, whereas CH3 was not able to sustain the drug release for 8 h. This may be attributed to the fact of increased pore forming agent concentration and smaller quantity of polymer used in the formulation which is not able to hold the drug within its matrix for a long time. On increasing the concentration of the pore forming agent, drug

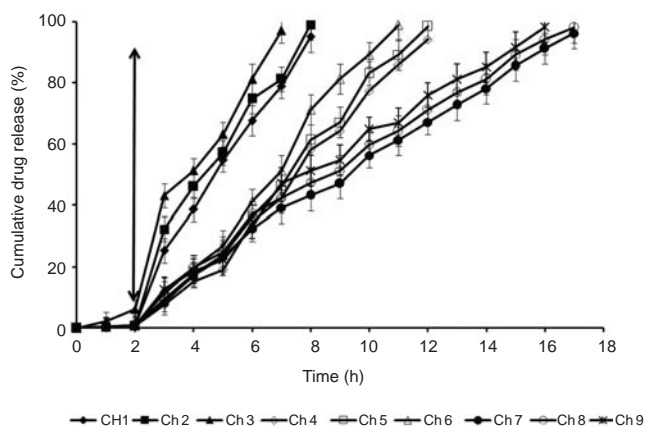


Fig. 4. *In vitro* drug release profile of all batches of MT loaded NPs mean  $\pm$  SD,  $n = 3$ .

release will increase because there will be more porous surface available for the drug to diffuse out.

The same effect was observed in case of other batches. But these batches were able to sustain the drug release up to 12 h, which is preferable for maintaining the drug concentration for a long period of time. Drug release at the end of 12 h was found to be  $94.2 \pm 2.6$  for CH4 and  $98.8 \pm 2.1$  for CH5. CH6 was not able to sustain the drug release for 12 h and released the maximum amount of drug load after 11 h ( $98.9 \pm 1.8$  %). Sustained effect was due to the increased amount of polymer prolonging the time for drug release.

In case of polymeric nanoparticles (CH7 to CH9), it was found that the prepared batches were able to sustain the drug release even for 18 h: CH7  $96.2 \pm 1.7$  %, CH8

Table IV. Release kinetics of MT from porous nanoparticles batches,

| Formulation code | R <sup>2</sup> |             |         | Korsmeyer Peppas (n) |
|------------------|----------------|-------------|---------|----------------------|
|                  | Zero-order     | First order | Higuchi |                      |
| CH1              | 0.9686         | 0.6956      | 0.7984  | 2.125                |
| CH2              | 0.9673         | 0.8125      | 0.8115  | 2.698                |
| CH3              | 0.9745         | 0.8513      | 0.8298  | 2.355                |
| CH4              | 0.9769         | 0.7874      | 0.8347  | 2.425                |
| CH5              | 0.9731         | 0.8125      | 0.8426  | 2.278                |
| CH6              | 0.9786         | 0.8347      | 0.7311  | 2.358                |
| CH7              | 0.9687         | 0.7891      | 0.7228  | 2.336                |
| CH8              | 0.9645         | 0.8042      | 0.6713  | 2.547                |
| CH9              | 0.9666         | 0.8188      | 0.8514  | 2.358                |

98.8 ± 1.8 % and CH9 96.9 ± 2.4 %. Hence, it can be concluded that the more the polymer used, the more sustained drug delivery can be obtained. Maintaining a desired polymer to pore forming agent ratio, a desired drug release profile can be achieved.

### Release kinetics

Release kinetics of the porous nanoparticles prepared is shown in Table IV. The best fit model representing the drug release from porous nanoparticles was of the zero-order. This is further confirmed by the Korsmeyer-Peppas model; the value of  $n$  is greater than 1, showing case II drug release or anomalous drug release, indicating that two or more drug release mechanisms are involved, that is, diffusion and erosion.

## CONCLUSIONS

Porous nanoparticles of metoprolol tartrate were obtained by spray-drying of chitosan solution using ammonium carbonate as a pore forming agent. Chitosan can be used as a carrier for the low dosed delivery system for single dose administration of metoprolol tartrate. Studies show that using a low pump inlet rate, small sized particles can be produced. Drug was successfully incorporated in porous nanoparticles by the dipping method, which can be used for many other, water-soluble drugs where drug entrapment is a tedious process. GPC clearly showed that chitosan was not degraded in terms of its molecular mass and could be used to produce spray-dried nanoparticles. DSC and FTIR studies showed that the drug and polymer used are compatible, ruling out any interactions. SEM confirmed the formation of open pores, which allow the media to easily go inside the porous structure of nanoparticles. TEM is in conformity with SEM studies. *In vitro* drug release studies showed that drug loaded nanoparticles were able to sustain the delivery of the drug even for 18 hours.

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## S A Ž E T A K

### Porozne nanočestice metoprolol tartarata dobivene pomoću sušenja sprejanjem: Razvoj, karakterizacija i evaluacija *in vitro*

MOHAMMED S. KHAN, GOWDA D. VISHAKANTE I HOSAKOTE G. SHIVAKUMAR

U radu je opisana priprava poroznih nanočestica metoprolol tartarata pomoću sušenja sprejanjem, koristeći amonijev karbonat za stvaranje pora. Da bi se spriječilo oslobađanje metoprolol tartarata u gornjem dijelu GI trakta, nanočestice su obložene polimerom Eudragit S100. Nanočestice podjednake veličine mogu se dobiti polaganim uklapanjem ljekovite tvari. Mikromeričke studije potvrdile su da su nanočestice zasebne i tečne. Proučavan je utjecaj sredstva za stvaranje pora na količinu uklopljenog lijeka, poroznost i *in vitro* oslobađanje. Povećanje količine sredstva za stvaranje pora povećava količinu uklopljenog lijeka, poroznost i brzinu oslobađanja ljekovite tvari. Oslobađanje metoprolola slijedi kinetiku nultog reda.

**Ključne riječi:** metoprolol tartarat, porozne nanočestice, sušenje sprejanjem, gel permeacijska kromatografija

*Department of Pharmaceutics, JSS College of Pharmacy, JSS University, Sri Shivarathreeshwara Nagara Mysore-570015, India*