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# PRELIMINARY INVESTIGATIONS FOR PROCESS OPTIMIZATION OF SPRAY DRIED CHITOSAN MICROSPHERE OF FELODIPINE*

# PRELIMINARNO ISPITIVANJE OPTIMIZACIJE PROCESA SUŠENJA SPREJEM HITOZANSKIH MIKROSFERA SA FELODIPINOM*

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*Invited paper/*Rad po pozivu

*Abstract*

Spray drying technique for formulation of microparticles compared to conventional methods is proved successful in pharmaceutical research due to unique features of rapid process, reproducibility, comfortable scale up and desired end product properties. The objective of the present investigation is to study the effect of various process parameters for formulation of polymeric microparticles by spray drying technique. Felodipine, a 1,4-dihydropyridine-derivative calcium channel blocking agent, is widely used for the treatment of hypertension, was taken as model drug. Polymeric concentration, drying chamber temperature, feed rate of solution into drying chamber and aspiration rate were optimized for felodipine loaded chitosan microparticles. The batches were formulated by varying each parameter at a time and keeping all other parameter constant. The microparticles were evaluated for % yield, entrapment efficiency, average particle size, particle size distribution, particle shape, true density, flow property and in-vitro drug release. The microparticles with higher polymeric concentration retarded burst release of drug. The higher temperature of drying chamber reduces the entrapment efficiency and increases the average particle size; however microparticles had irregular particle shape. Faster feeding of solution caused sticking of polymeric solutions on the wall leading to poor yield, which may be due to insufficient drying time. The lower aspiration rate also caused sticking of feed on wall and higher aspiration caused conveying of particles to fine collector filter bag leading to poor yield, hence the optimum aspiration is pre-requisite for good yield. The results of % yield and entrapment efficiency were found varied in different batches, which indicates that selected process parameters is significantly affecting the process. At the end, it may be concluded that the microparticles with desirable physical characteristics and drug release may be formulated by systemically optimizing critical process parameters of spray drying technique.

*Key words*
Chitosan, Spray drying, Microparticle, Felodipine, Effect of process parameters

*Ključne reči*
hitozan, sušenje sprejem, mikročestice, felodipin, efekat na parametre procesa

## *INTRODUCTION*

Felodipine is a, dihydropyridine derivative, calcium channel antagonist which causes vasodilation. It has negative inotropic effect and also interacts with calmodulin. It is widely used in the treatment of hypertension. Felodipine is rapidly absorbed after oral administration, but due to its first pass effect, the oral bioavailability is very low (15%). It is extensively metabolized in liver and its 70% of metabolite is excreted in urine and remaining drug in feces. Besides that felodipine is having poor water solubility which causes dissolution process as rate limiting step and eventually affect the absorption of the drug [1-5]. For the drugs which are having low bioavailability through oral route. Researchers have explored other routes of drug delivery like Nasal, Buccal, Transdermal etc.

Nasal drug delivery has now been recognized as a very promising route for delivery of therapeutic compounds including biopharmaceuticals. The nasal cavity offers a large, highly vascularised subepithelial layer for efficient absorption. Also, blood is drained directly from nose into the systemic circulation, thereby avoiding first pass effect. Initially major drawbacks associated with the nasal drug

delivery were short residence time of the formulation within the nasal cavity coupled to the low permeability. As compared to conventional nasal formulation, mucoadhesive microparticles have higher residence time in nasal cavity. Microparticles absorbing water from the cells due to which cell get shrink and open the cell junctions to increases the permeability of mucosa [6]. Therefore, the attention shifted to the evaluation of mucoadhesive polymers, some of which would even demonstrate additional permeation enhancing capabilities such as chitosan.

Natural polymers have gained a lot of consideration in the field of drug delivery because of their distinguished physical and biological properties. Chitosan is among one of the widely explored polymer in research. Chitosan is obtained by the deacetylation of chitin which is obtained from the exoskeleton of crustaceans such as crabs, shrimps, prawns, lobsters and cell walls of some fungi such as aspergillus and mucor. There are some unique properties of chitosan which drawn attention with in pharmaceutical and biomedical applications. It is having cationic nature which results in its mucoadhesivity with cell membrane, biodegradability, biocompatibility, non-toxicity and absorption-enhancing effect. Wide range of derivatives of chitosan can be prepared because of presence of reactive functional groups in chitosan which offers great opportunity for chemical modifications. Chitosan microparticles can be used for both systemic as well as local therapy. There are majorly four approaches for the preparation of chitosan microspheres- ionotropic gelation method, simplex or complex coacervation method, emulsification solvent evaporation method and spray drying method [7-13].

Spray drying is the continuous transformation of feed from a fluid state (i.e. solution, suspension, or emulsion) into dried particulate form by spraying the feed into a hot drying chamber using spray nozzle causing evaporation of solvent from droplet, resulting in formation of microparticles. Spray drying process have merits like rapid process, reproducibility, comfortable scale up and desired end product properties that can be designed to virtually any capacity required. It can be used with both heat-resistant and heat sensitive products because of short time duration of high heat application. Few shortcomings include limited versatility in producing particles or structures with the complex morphologies and rapid drug release rates often exhibiting a burst effect. Spray drying process mainly involves following steps in sequence: feed stock preparation, atomization, droplet drying and separation (by cyclone separator). Critical process parameters of spray dried microparticles are as- inlet temperature, polymeric concentration, feed rate, atomization air pressure and aspiration. The above mentioned process parameters are required to optimize for obtaining the microparticles with desirable properties like particle size, particle morphology, yield, entrapment efficiency, derived property like flow ability and in-vitro drug release pattern.

**Thus, present work was aimed to** study the effect of process parameters of Spray drying technique for the formulation of felodipine loaded chitosan microparticles.

## *MATERIALS AND METHODS*

### *Materials*

Felodipine was gifted by Torrent Research Center (Ahmedabad, Gujarat). Chitosan was procured from HiMedia Laboratories Pvt. Ltd. (Mumbai). Mannitol, Propylene Glycol and Glacial acetic acid were procured from Central Drug House Ltd. (New Delhi). Ethyl Alcohol (Absolute) was procured from Ureca Consumers Co. Op. Stores Limited (Ahmedabad). All the reagents were of analytical grade.

### *Preparation of Spray dried Microparticles*

Polymeric microparticles of Felodipine were prepared by Spray drying technique. Chitosan was dissolved in 1% acetic acid solution while Felodipine was dissolved in Ethanol (absolute). Both solutions were miced in 1:1 ratio for 30 min. 250 ml of resultant mixture was taken as feed solution which was sprayed at 0.5 bar atomization pressure using two fluid nozzle in Spray dryer (Spray Mate, JISL, Mumbai) to formulate microparticles under various process conditions (inlet temperature, amount of polymer, feed rate and aspiration) as shown in Table 1. The microparticles obtained from the collecting vessels were stored in glass vials for further evaluation. The formulation and process parameters were selected to study the effect of drug: polymer ratio, aspiration, inlet temperature and feed rate on various characteristics of microparticles.

*Table 1 Formulation composition and spray conditions of Felodipine loaded Chitosan Microparticles*

| Batch No. | A1 | A2 | A3 | A4 | A5 | A6 | A7 | A8 | A9 |
|---|---|---|---|---|---|---|---|---|---|
| Drug (mg) | 375 | 375 | 375 | 375 | 375 | 375 | 375 | 375 | 375 |
| Chitosan (mg) | 750 | 1500 | 2250 | 1500 | 1500 | 1500 | 1500 | 1500 | 1500 |
| | | | | Process Parameters | | | | | |
| Inlet Temp. (°c) | 160 | 160 | 160 | 140 | 200 | 160 | 160 | 160 | 160 |
| Aspiration* | 1200 | 1200 | 1200 | 1200 | 1200 | 1500 | 900 | 1200 | 1200 |
| Feed Rate (RPM) | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 40 | 20 |

* Aspiration in terms of units mentions in spray dryer

### ***Characterization of microparticles***

### *Particle size and Particle Size Distribution*

Particle size and particle size distribution of microparticle was measured by laser diffraction method using wet dispersion system Hydro 2000 S of Mastersizer 2000 Ver. 5.60 (Malvern Instruments, UK). Samples for size analysis were prepared by dispersing microparticles in 1-butanol. Dispersed microparticles were added to sample cell containing 1-butanol until the obscuration limit between 10-20% was achieved. The size of microparticles was evaluated with refractive index of particle and dispersant as 1.57 and 1.399 respectively. The average particle size (d50) was expressed as the volume weighted mean in micrometers [20].

*Percentage Yield*

The percentage yield of microparticles was determined from the ratio of total amount of dried solid microparticles obtained (A) to the total amount of solid material (drug and polymer) (B) taken in feed solution to be sprayed. The results were expressed as percentage according to the Eq. 1 mention below [21].

$$\%Yield = \frac{A}{B} x100 \quad (1)$$

*Entrapment efficiency*

To determine EE or content of felodipine in microparticles was measured by extracting drug from microparticle using known quantity of methanol. Microparticles were weighed and mixed in methanol; resultant suspension of microparticle was crushed in mortar pestle and then sonicated for 1 h, for completely leaching out of the drug in methanol. The mixture was filtered and assayed for the felodipine content after appropriate dilution by UV-Visible spectrophotometer (UV 1800 Shimadzu Scientific Instrument, Japan) at 362 nm. For each formulation, assay was replicated three times and average amount of felodipine was used to calculate the drug loading as per formula mention below in Eq. 2-

$$\%Entrapment\ Efficiency = \frac{P_E}{T_E} x100 \quad (2)$$

Where PE refers the amount of Felodipine (practically) entrapped in microparticles and TE refers the initial amount of Felodipine added for preparation of microparticles [22].

*Flow property*

The flow property of formulations was investigated by computing Carr's index using USP-1 Bulk Density Apparatus (Model: VTAP/ MATIC-II, Mumbai, India). The known quantity of sample was filled in a graduated measuring cylinder, tapped mechanically with constant speed and bulk volume and tap volume were measured which used for calculating bulk density (BD) and tapped density (TD) of formulations. The BD and TD were used to determine Carr's index as per the following Eq. 3. [23, 24]-

$$Carr\ sIndex = \left[\frac{(TD-BD)}{TD}\right] x100 \quad (3)$$

*In vitro Drug Release study*

An in vitro drug release study of microparticles was performed using automatic dissolution test apparatus (TDT-08L with Electrolab Fraction Collector, Dissolution Tester (USP), Electrolab) according to the USP basket apparatus. The weighed quantity of microparticles (equivalent to dose of felodipine) was taken in basket and covered with muslin cloth. Temperature of the dissolution media (200 ml phosphate buffer, pH 7.4) was maintained at 37±0.5 °C. The samples (5 ml) were taken at predetermined time intervals (i.e. 0.5, 1, 2, 3, 4, 6, 8, 10, 12 h) and replaced with the same volume of dissolution medium. Felodipine content in the dissolution samples was measured by UV spectrophotometric analysis at 362 nm. Drug release in 60 (t60) and 480 (t480) were taken as evaluation parameters for studying the effect of formulation and process parameters on characteristics of microparticles.

## *RESULTS AND DISCUSSION*

*Effect of Drug : Polymer ratio*

The effect of change in Drug: polymer ratio (Formulation A1 to A3) on the properties of microparticles was shown in Figure 1.

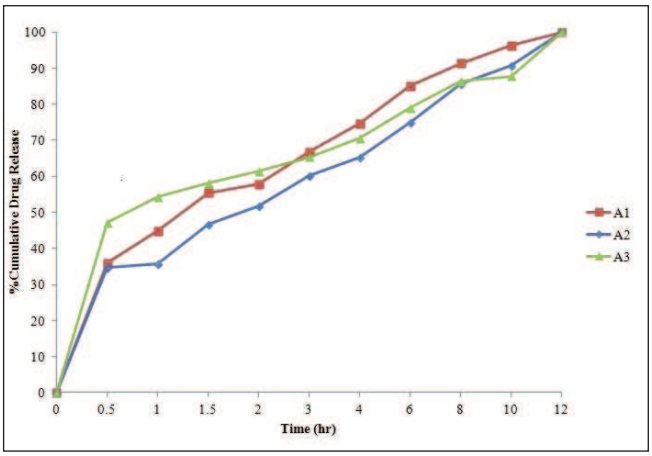


*Fig. 1 Effect of Polymeric Concentration on Drug Release*

It was found that as the amount of polymer was increased in the spraying solvent, the particle size was increased. This may be due to increment in the viscosity of polymer solution. At higher concentration of chitosan, resulting in, there might be formation of larger droplet at fixed atomization pressure which ultimately produces comparatively bigger particles. The increase in particle size results in improving the flow property of the microparticles [25].

Drug entrapment efficiency of microparticles was also increased with the increase in polymeric concentration. Increase in polymer concentration augmented the polymer matrix of microparticles and hence drug release property at both initial (t60) as well as final (t480), time points was decreased. This might be due to formation of more polymeric matrix which prevents the diffusion of drug from the microparticles. All the batches were showing higher drug release due to rapidly adsorbing water characteristics of chitosan; causes higher swelling which leads to faster drug release [26].

As the polymeric concentration of feed solution was increased, the yield of microparticles was first increased and then decreased. The amount of polymer in feed solution affects the droplet size which eventually affects the yield of microparticles. Small size microparticles formed in the process due to lower polymer concentration could not be separated from air stream in cyclone separator and collected in dust collector as wastage. The larger droplet size, due to increase in polymer concentration, also leads to decrease in yield. This may be due to incomplete drying of droplets before reaching at the wall of drying chamber which led to deposition of droplets on the wall as film and results in decrease in yield of microparticles.

*Effect of temperature*

Figure 2. shows the effect of temperature on the properties of microparticles formulations (A2, A4 and A5).

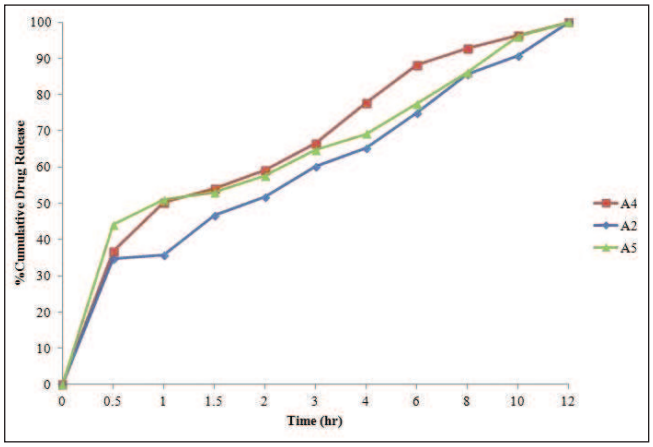


*Fig. 2 Effect of Temperature on Drug Release*

Yield of microparticles was decreased at both lower and higher inlet temperature. At lower temperature there may be improper drying of droplets which results in their deposition on the wall of drying chamber and make a film and eventually decrease in yield. While at higher inlet temperature the evaporation of feed solution occurs prior to spray causing deposition of polymer in the spray gun, which ultimately results in the improper spraying leading to reduction in the yield of microparticles. This also negatively affects the entrapment efficiency of the microparticles in polymeric microparticles.

The size of microparticles was decreased with the increase in temperature and which ultimately decreases the flow property of microparticles. Effect of increase in inlet temperature was shown at initial time points (t60) while there was no significant difference in drug release at later time points (t480).

*Effect of aspiration*

The effect of aspiration on the properties of microparticles was shown in Figure 3.

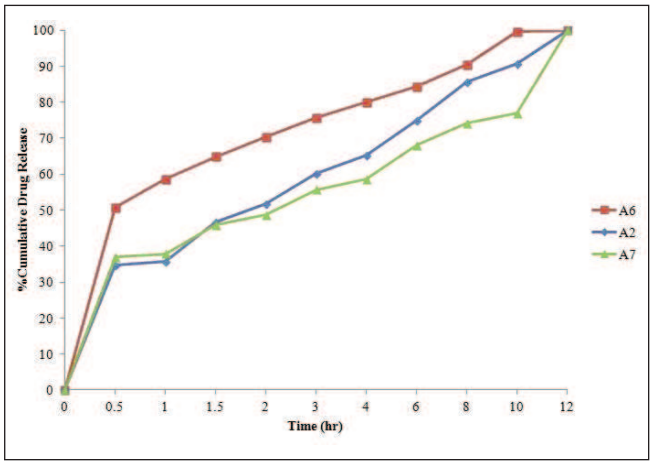


*Fig. 3 Effect of Aspiration on Drug Release*

The yield of microparticles was found decrease at both lower and higher aspiration values. At lower aspiration, the flow of air was not capable to make streamline flow of the droplets while drying which led to their deposition on the wall of drying chamber and results in lower yield. While at higher aspiration, there was a large drag on the microparticles which prevent their retention in the cyclone separator and go to the dust collector as waste.

The particle size of the microparticles was decreased with increase in the aspiration which ultimately decreases in the flow property of the microparticles. The drug release was increased at both t60 and t480 with the increase in the aspiration.

*Effect of feed rate*

Figure 4. is showing the effect of feed rate on the properties of the microparticles.

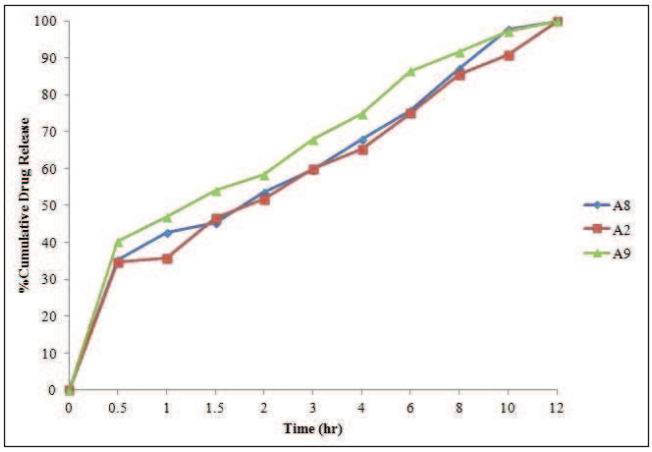


*Fig. 4 Effect of Feed Rate on Drug Release*

The yield of microparticles was decreased at both low as well as high feed rate. At low feed rate, the applied atomization pressure was capable to break the feed solutions in fine droplets. While larger droplets were formed at higher feed rate as the applied atomization pressure was not sufficient for large feed volume of spraying solution.

The smaller particles could not collect as product and go to dust collector while larger particles got deposited on the wall of drying chamber. This also affects the particle size of the microparticles which increase with the increase in the feed rate of solution. No significant effect was observed on the flow property and drug release from microparticles at both time points.

*CONCLUSION*

Microparticles developed using spray drying technique has more potential for industrial applicability in formulation development compared to conventional technique. The developed polymeric microparticles of felodipine using chitosan shown narrow size distribution and their characteristics can be controlled by various formulation and process parameters. From the results of all the formulated batches, it can be concluded that each process and formulation parameters have impact on properties of microparticles which varies with the level of parameters. Thus, it can be concluded that before going to optimization process, it is necessary to study the limits of all the process and formulation related parameters.

## *Sažetak*

Tehnika sušenja sprejem za formulaciju mikročestica pokazala se uspešnom u odnosu na standardne metode koje se koriste u farmaceutskom istraživanju, zbog svojih jedinstvenih karakteristika: brz proces, reproducibilnost, zadovoljavajući scale up kao i željena svojstva krajnjeg proizvoda. Cilj ovog istraživanja je da se ispita uticaj različitih parametara procesa za formulaciju polimernih mikročestica tehnikom sušenja sprejem. Felodipin (1,4 - dihidropiridinski derivat), blokator kalcijumovih kanala, koji se često upotrebljava za lečenje hipertenzije, uzet je kao model leka . Koncentracija polimera, temperatura komore za sušenje, brzina dodavanja rastvora u komoru za sušenje i protok vazduha su optimizovani za hitozan mikročestice napunjene felodipinom. Serije su formulisane tako da postoji varijacija samo jednog parametra, dok su za ostale ostavljeni konstantni uslovi. Parametri koji su testirani za mikročestice su: prinos (%), efikasnost inkapsulacije, distribucija i prosečna veličina čestica, oblik čestica, realna gustina, protok vazduha, kao i in vitro oslobađanje leka. Mikropartikule sa višim koncentracijama polimera imaju produženo oslobađanje leka. Viša temperatura komore za sušenje smanjuje efikasnost inkapsulacije, a povećava prosečnu veličinu mikročestica, međutim čestice imaju nepravilan oblik. Brže dodavanje rastvora uzrokovalo je lepljenje polimernog rastvora na zid uzrokujući manji prinos, što može imati veze sa nedovoljnim vremenom sušenja. Slabiji protok vazduha takođe uzrokuje lepljenje čestica na zid suda, dok veći protok uzrokuje eliminaciju čestica u filter vreću koja sakuplja nečistoće, što opet reziltuje manjim prinosom. Dakle, optimalni protok vazduha je preduslov za dobar prinos. Rezultati izraženi kao procenat prinosa i efikasnost inkapsulacije, variraju u različitim serijama, što nam indikuje da ovi parametri značajno utiču na dati proces. Na kraju, može se zaključiti da mikročestice sa poželjnim fizičkim karakteristikama i stopom oslobađanja leka mogu biti formulisane sistematskom optimizacijom kritičnih parametara postupka tehnike sušenja sprejem.


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