*Research Article*

# Micropellets: A promising strategy for controlled release of lansoprazole

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## Abstract

**Objective:** We aimed to develop a suitable micropellet delivery system for Lansoprazole, a highly potent proton pump inhibitor and acid-unstable physiologically active anti-secretory compound. Although clinically manifested to be highly effective for treating acid reflux-related diseases, poor water solubility and short gastric retention time, typically does not provide extended period of relief. **Materials and method:** Micropellets of the drug was prepared using ionotropic gelation technique, where gelation of anionic sodium alginate, the primary polymer, was achieved with oppositely charged counter ion to form microparticles and subjected to several characterization studies. **Results:** Scanning electron microscopy of the micropellets exhibited spherical shape with mean size range 300 to 800 μm. The formulation showed higher entrapment efficiency of 98.4%. The drug release profile obtained for formulation indicated that it is an ideal formulation for administration for every 24 h, as it released 42.55% of the embedded drug in 9 hours. **Conclusion:** Data presented herein suggest micropellets as a suitable vector of Lansoprazole, however, pre-clinical studies in suitable animal models would further establish the translational utility of the prepared formulation.

***Keywords:*** Micropellets, Ionotropic gelation, Lansoprazole, Gastrointestinal reflux disease

## Introduction

Lansoprazole is a proton pump inhibitor (PPI) which is an effective and well-tolerated treatment option in the management of acid-related disorders. Lansoprazole is a proton pump inhibitor (PPI) which inactivates the final step in the gastric acid secretion pathway in gastric parietal cells in a dose-dependent manner (Petersen and Schmutzler, 1999). Bioavailability is 85% after the first dose the highest among PPIs and acid inhibition is swift, resulting in rapid relief of symptoms (Pillay and Fassihi, 1999). Lansoprazole also exhibits antibacterial activity against Helicobacter pylori in-vitro. It is usually administered as conventional capsules containing 15-30 mg, once a day. Drug requires enough dosing by oral route due to its intrinsic limited half-life, sustained release formulation administration will lead to decline of dosing rate of recurrence and in converse develop patient conformity. It deserves merit to which there is increase in bioavailability inspite of drug undergoing substantial first pass metabolism (Nagata et al., 1995; Florence, 1997; Ulrich and Matthias, 2005).

Micro pellets are solid particles of various shapes (spherical to oval and spheroid) of size ideally less than 125 micron that can be suspended in a suitable aqueous vehicle and injected by 17-20 Gz needle. Micropellets have a tremendous potential as depot formulations. In sterilized dosage form tools merely suspensions of (lipophilic) drug particle and micro element using biodegradable polymers are used as depot principles (Ulrich and Matthias, 2005; Roy and Das, 1989).

Micropellets that use parenterally acceptable polymers ensure that the entire slow release strategies (Dashevsky et al., 2004) normally used for solid dosage forms can now be made available for sterile products. Using these approaches, release profiles ranging from days to months and even pulsed release can be obtained at wish (Lambert et al., 2000,

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Bechgaard and Nielson, 1978).

The aim of the present study is to develop a suitable microparticulate system of Lansoprazole for control release delivery system. In the projected technique of ionotropic gelation method, globular micropellets with a narrow particle size distribution and low friability could be prepared with high yield and drug content.

## Materials and method

Lansoprazole was obtained as gift sample from Hetero drugs limited, Hyderabad, India. Sodium alginate was obtained from Loba chemie, Mumbai, India. Calcium chloride dehydrate obtained from Glaxo Smith Kline Pharmaceuticals Ltd, Mumbai; Ethyl cellulose Colorcon, Goa, India. All ingredients used were of analytical grade.

**Preparation of lansoprazole loaded micropellets**

The micropellets of lansoprazole were prepared by using ionotropic gelation technique. In this method weighed quantity of drug was dispersed uniformly in aqueous mucilage of sodium alginate using mechanical stirrer maintaining the speed at 500-600 rpm. To this dispersion the ethyl cellulose was mixed in s proportions and the entire mixture was stirred for 30 min. The micropellets were formed by dropping the bubble free dispersions through a glass syringe with flat tip needle (20G) into a gently agitated calcium chloride solution (Narkar et al., 2010). The gelled micropellets were cured for 1 hour to complete the gelation reaction before being filtered and washed thoroughly with distilled water and isolated micropellets were dried at room temperature and then in hot air oven at 60°C for 6 h for further drying (Millili and Schwartz, 1990; Lim and Wan, 1997).

**Table 1**. Formula for preparation of micropellets

| S. No. | Ingredients | Quantity |
|---|---|---|
| 1. | Drug (Lansoprazole) | 600 mg |
| 2. | Ethyl cellulose | 600 mg |
| 3. | Sodium alginate | 1000 mg |
| 4. | Calcium chloride | 2500 mg |
| 5. | Acetone | 25 ml |
| 6. | Distilled water | q.s |

**Characterization of micropellets**

**Drug entrapment efficiency**

Ten mg of micropellets (# 22 sizes) were accurately weighed and dissolved in 10 ml of 0.1M NaOH and sonicated to suspend. Final volume was finished up to the mark by 0.1M NaOH and an aliquot from the filtrate was analyzed after suitable dilution, using UV/Visible spectrophotometer (Shimadzu® 1700, Japan) at 292nm. Drug entrapment efficiency (DEE) was calculated according to the formula:

% DEE= (Actual drug content/ Theoretical drug content) X 100

**Surface accumulation study**

This study was conducted to estimate the amount of drug present on the surface of micropellets which may show immediate release in the dissolution media. 10 mg of micropellets (# 22 sizes) were suspended in 10 ml of phosphate buffer (pH 6.8), simulating the dissolution media. The samples were stunned briskly for 15 min in a mechanical shaker. The quantity of drug trickle out from the exterior was analyzed spectrophotometrically at 292 nm (Lim and Wan, 1997).

**Particle size determination**

The particle size of a pharmaceutical substance is strictly maintained in order to get optimal biological activity. Sieves were arranged in a nest with the coarsest at the top. A sample (10 gm) of the powder was placed on the top sieves. This sieve set is preset to the mechanical shaker device and shaken for a certain period of time (20 minutes). The powder retained on each sieve was weighed. Frequently, the powder was assigned the mesh number of the screen through which it passes or on which it is retained. It is articulated in terms of arithmetic or geometric mean of the 2 sieves retained matter. Average particle size was calculated using the formula given below (Bansal et al., 1993; Ragnarsson et al., 1992):

$d_{avg} = \sum dn / \sum n$, where, n= frequency weight

d= mean diameter

**Scanning electron microscopy**

Morphology details of the specimens were determined by using a scanning electron microscope (SEM), Model JSM 35CF, JEOL, Japan. The samples were dried thoroughly in vacuum dessicator before mounting on brass specimen studies. The samples were scale on specimen studies with double sided adhesive tape, and gold-palladium alloy of 120Ao kness was coated on the sample using sputter coating unit (Model E5 100 Polaron U.K.) in Argon ambient of 8-10 Pascal through plasma voltage about 20 MA (Nagata et al., 1995; Roy and Das, 1989). The sputtering was done for nearly 3 minutes to obtain uniform coating on the sample to enable good quality SEM images. The SEM was managing at small accelerating voltage of concerning 15 KV with load current of concerning 80 MA. The condenser lens position was maintained between 4.4-5.1. The objectives lens orifice have a diameter of 240

microns and the working distance WD = 39 mm (Bechgaard and Nielson, 1978; Turkan et al., 1991).

**Micromeritic study of lansoprazole micropellets**

To a graduated cylinder accurately weighed quantity of the micropellets (W), was carefully poured and the volume (Vo) were measured. Then the graduated cylinder was closed with lid and 100 times taped from a constant height and after that, the volume (Vf) were measured and continued operations till the two consecutive readings were found to be the difference of not more than 2.0%. The bulk density, and tapped density were calculated using the following formula (Tomofumi et al., 2001):

Bulk density = W / Vo

Where, W = weight of the powder

Tapped density = W / Vf Vo= initial volume;

Vf = final volume

***Angle of repose***

At a specified height funnel was kept vertically in a stand below which a paper placed on a horizontal surface. The bottom of the funnel was closed and filled with 15 gm of sample powder in funnel. Then funnel were opened to release the powder on the paper to form a smooth conical heap. The height of the heap was measured by using scale.

Moisture content

Weighed quantity of the micropellets were placed in watch glass and dried to constant weight in a hot air oven at 25-300C. The moisture content (MC) was deduced as difference between the initial (Wo) and final weight (Wf) of the micropellets expressed in percentage and calculated by given formula (Millili and Schwartz, 1990):

**Disintegration time**

Disintegration study was performed in 0.1N HCl and phosphate buffer (pH 6.8) by tablet disintegration test apparatus. Sieves of 710 mm mesh size were packed at the top and bottom of the tube of apparatus. 50 mg micropellets were filled in each tube; they are inserted in standard tablet disintegration tester. The disintegration time of four dried samples at 370C was determined at a speed of 30 dips.

**Friability**

Resistance to abrasion was determined using USP method for measurement of tablet friability. Accurately weighed quantity of micropellets sample was placed in Roche friabilator. Drum was rotated 100 times, and micropellets were removed. After dedusting, weight loss from the sample was measured by sieving the micropellets through #85 sieves.

$$\textbf{Friability}\ (\%) = \frac{\text{Final weight- Initial weigh}}{\text{Final weight}} \times 100$$

**Gastric acid resistance study**

The release of drug from the developed formulations in the environment of gastrointestinal tract was determined using the USP (XXIV) dissolution apparatus II by double beam UV/Visible spectrophotometer (Shimadzu® 1700, Japan). Capsules containing micropellets equivalent to 30 mg of Lansoprazole in beaker containing 900ml 0.1 N HCl as dissolution media maintained at 37 ± 0.5°C and 75 rpm. After 1h the medium was drained without losing the pellets transfer it to a filter paper and dry the pellets by blotting with filter paper. Pellets were transferred into 100 ml volumetric flask; 40 ml of 0.1 M NaOH was added and sonicated to dissolve. Further it was diluted up to 100 ml with 0.1 M NaOH.

Aliquot of samples were withdrawn assessed spectrophotometrically at a wavelength of 292 nm with a UV spectrophotometer.

***In-vitro* dissolution studies**

A drug is expected to release from the solid dosage forms (granules, tablets, capsules etc) and immediately go into molecular solution. This process is called as dissolution. The dissolution study was carried out according to the USP (XXIV) paddle method, for micropellets (in 0.1 N HCl for 2 h and pH 6.8 phosphate buffer after 2 h) to mimic the cumulative release of drug in stomach, as per the USP general drug release standard for delayed-release dosage form specifications with a paddle speed of 100 rpm at 37 ± 0.5°C in 900 ml of dissolution medium (Dressman and Reppas, 2000).

Capsules containing micro pellets equivalent to 30 mg of Lansoprazole taken in beaker containing 900 ml of 0.1N HCl as dissolution media maintained at 37 ± 0.5°C and 100 rpm. After 1h the medium was drained without losing the micropellets and to the beaker 900 ml of pre heated buffer solution of pH 6.8 was added, study was further continued for 9h at 75 rpm. Aliquot of samples were withdrawn at regular interval of time which was replaced by the same amount of fresh medium and was assessed spectrophotometrically at a wavelength of 292 nm with a UV spectrophotometer.

**Drug release kinetics**

In order to understand the mechanism and kinetics of drug release, the outcome of the in-vitro dissolution study of the micropellets was fitted with various kinetic equations, the following plots were made: cumulative % drug release vs. time (zero order kinetic model); log cumulative of % drug remaining vs. time (first order kinetic model); cumulative % drug release vs. square root of time (higuchi model) log

cumulative % drug release vs. log time (korsmeyer model) and cube root of drug % remaining in matrix vs. time (hixson-crowell cube root law) and the values of co-efficient of correlation (r2) values were calculated for the linear curves obtained by regression analysis of the plots (Korsmeyer and Peppas, 1981).

## Results and discussion

Lansoprazole micropellets formulated, using ethyl cellulose as release retardant in various concentration. These micropellets were prepared in an environment which is free from organic solvents, by tumbling a mixture of colloidal copolymer dispersal, the dispersed drug lansoprazole, and mucilage of sodium alginate in calcium chloride solution, which acted while a counterion. The globule instantly formed gelled sphere-shaped in shape owing cross linking of calcium ion with the sodium ion which remained ionized in the solution. Particle size can be varied by adjusting the height of the syringe from the level of counterion solution, compression force on the hypodermic needle. The gel particles were alleviated to get amply toughened and then strained and dried. The colloidal polymer particles fused into the polymer matrix during drying with the drug being dispersed in the latex. Lansoprazole meets all the ideal characteristics to formulate in the form of oral drug delivery system. The micropellets thus formed using three different polymers did show significant results on evaluation. Also it was found that with the increase in harvesting time, the micropellets formed in calcium chloride solution in turn decrease the drug entrapment efficiency.

### Drug entrapment efficiency

Formulation prepared with ethyl cellulose shows significant high entrapment efficiency of drug which confirms its rigidity.

### Surface accumulation study

These studies considered as a parameter giving an indication of the amount of drug on the surface of the micropellets devoid of appropriate sting. With the increase in the copolymer concentration % surface accumulation decreased significantly owing to high entrapment of drug in the impenetrable system of polymers.

### Particle size determination

The size of the micropellets ranged between 300 µm to 800µm. The particle size distribution was uniform and narrow. It can be estimated that with further change in processing parameters the particles would change from micro to granular level.

### Scanning electron microscopy

The scanning electron micrograph (SEM) (Figure 1) shows the micropellets being discoid in shape. SEM of prepared formulation indicated that the micropellets are spherical in shape and exhibited bridging. It can be concluded that the roughness is due to the density of the matrix which in turn justifies its sustained release. The impenetrable association of drug-polymer-copolymer augment the tortuosity, as apparent from Figure 1. Thus, impediment the release of the drug and retarding the penetration of water required to make the micropellets swell for disintegration.

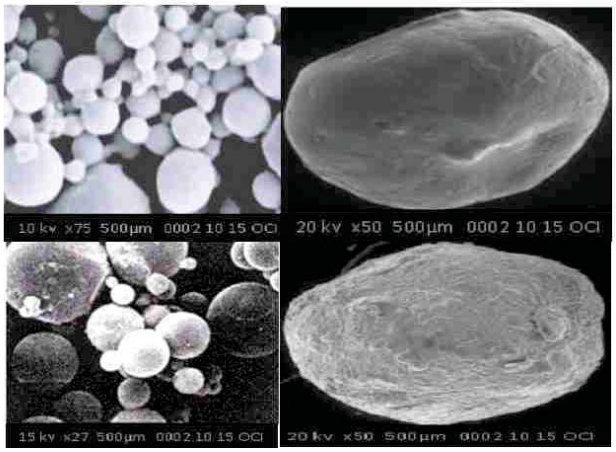


**Figure 1**. SEM photographs of Lansoprazole micropellets

### Micromeritic study of lansoprazole micropellets

The micromeritic properties of micropellets are tabulated in Table.2. The flow properties, represented in terms of angle of repose and hausner ratio of the micropellets, were much improved over those of pure drug crystals and confirm better flow and packing properties. Thus, the micropellets if tableted or encapsulated necessitate fewer amounts of lubricants and guarantee crouch production cost primary to its feasibility for large scale production.

### Determination of moisture content

Low moisture content in all the micropellets indicates the effectiveness of the optimized drying condition. Low down wetness point guarantees improved stability of the drug in the micropellets.

### Disintegration studies

There was no disintegration observed in 0.1N HCl, even though the samples were held in reserve for overnight in the medium. The ionic character of the polysaccharide resulted in pH dependant disintegration of the micropellets. Faster disintegration will result into more number of smaller particles in the dissolution medium. This will effect in an immense increase in surface area that donate largely to the augmented water solubility.

### Friability studies

Friability studies are performed to check resistance to abrasion, the results of the study is reported in Table 2 revels that friability ranges 0.3-1.2 which are within standard limits.

**Table** 2. Various Characterization Parameters for Micropellets Containing Lansoprazole

| S. No. | Parameters | Observation |
|---|---|---|
| 1. | Percentage yield (%)* | 78 ± 4.10 |
| 2. | Entrapment Efficiency (%)* | 74 ± 3.85 |
| 3. | Surface accumulation study (%)* | 1.567 ± 0.64 |
| 4. | Mean diameter | 346.64 ±2.05 μm |
| 5. | Bulk density (g/ml)* | 0.65 ± 0.06 |
| 6. | Tapped density (g/ml)* | 0.70 ± 0.05 |
| 7. | Compressibility index (%)* | 7.07 ± 0.82 |
| 8. | Flowability | Excellent |
| 9. | Hausner ratio* | 1.07 ± 0.24 |
| | | Excellent |
| 10. | Angle of repose* | $26.56^0$ ±1.85 |
| 11. | Moisture content (%)* | 0.91 ± 0.92 |
| 12. | Disintegration time (min)* | 34 ± 4.28 |
| 13. | Friability (%)* | 0.3 ± 0.02 |
| 14. | Gastric acid resistance study* | 98.01± 2.01 |

All values are mean ± S.D. for n=3

***In-vitro* dissolution studies**

The dissolution rate studies for each of the formulation were performed in order to assess the effect various process parameter and techniques on release contour. In dissolution studies, 900 ml solution of 0.1N HCl was occupied for 1 hour and pursue by 900 ml phosphate buffer pH 6.8 to imitate the cumulative release of drug in stomach.

Factors such as particle size, drug loading, polymer composition and process parameters govern the drug release from micropellets. The original drug crystals showed a faster release showing about 98% drug releases within 2 h in comparison to the microencapsulated form of the drug.

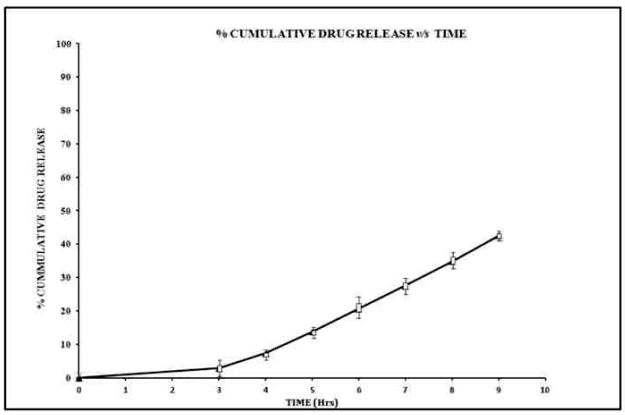


**Figure 2**. *In Vitro* drug release profile of micropellets

Predominantly, the drug release followed passive diffusion technique. On releasing, the drug present on the surfaces leaves behind pores or channels, through which diffusion of the drug present in the inner matrix of the micropellets occurred. Due to lose drug present on the surface of the micropellets (Surface Accumulation) the in vitro release profile obtained indicated a biphasic prototype i.e. initial fast release pursued by a sustained pattern (Table 3; Figure 2).

The drug release profile obtained for formulation indicated that it is an ideal formulation for administration for every 24 h, as it released 42.55% of the embedded drug in 9 hours.

**Table 3**. *In Vitro* drug release profile of Micropellets

| S. No. | Time(Hrs) | % Cumm. Drug release* |
|---|---|---|
| 1. | 3 | 2.91 ± 0.77 |
| 2. | 4 | 7.33 ± 1.08 |
| 3. | 5 | 13.79 ± 2.01 |
| 4. | 6 | 20.62 ± 2.45 |
| 5. | 7 | 27.63 ± 1.98 |
| 6. | 8 | 34.83 ± 3.05 |
| 7. | 9 | 42.55 ± 2.06 |

**Drug release kinetics**

The values of co-efficient of correlation (r) were calculated and were found to be linear for first order release as compared to zero order. Cumulative % drug released was subjected to curve fitting data using PRISM software. The facts subsist preeminent fitted to Korsmeyer and Peppa's model as well as good regression co-efficient was observed (Figure 3). This indicates that the release of the drug occurs by diffusion following non-fickian transport mechanism.

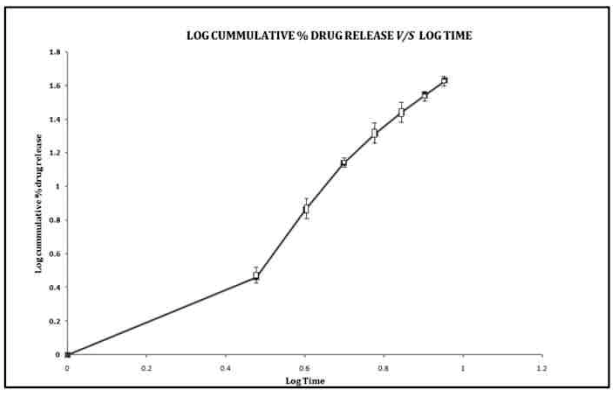


**Figure** 3. Dissolution kinetics and the model fittings (Korsmeyer and Peppa's model)

## Conclusion

The study was undertaken with an aim to develop sustained

release micro pellet dosage form for Lansoprazole, which is a potent proton pump inhibitor and is one of the most widely used drug for treating mild and severe ulcers. Sustained release micropellets containing water insoluble drug were successfully prepared employing ionotropic gelation technique entirely avoiding the use of organic solvents. Separately as of natural water soluble polymer, the employing of copolymer additionally prolongs the release of the drug.

Considering the end product, the micropellets could be administered as prepared or could be compressed into tablet or filled in capsule shell. The complete progression is practicable in an industrial scale and demands pilot study.

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