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# FORMULATION AND IN VITRO EVALUATION OF LANSOPRAZOLE MICROPELLETS

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**Running Title: Formulation and evaluation of Delayed Release micropellet for Lansoprazole**

**ABSTRACT:** Pellets are agglomerates of fine powders or granules of bulk drugs and excipients. They consist of small, free flowing, spherical or semi-spherical solid units, typically from about 0.5mm to 1.5mm, and are intended usually for oral administration. Pellets can be prepared by many methods, the compaction and drug-layering being the most widely used today[1]. The study was undertaken with an aim to develop delayed release micropellet dosage form for Lansoprazole which is a benzimidazole anti ulcer agent and is one of the most widely used drugs for treating mild and severe ulcers. The approach of the present study was to make a comparative evaluation among these polymers and excipients and to assess the effect of physicochemical nature of the active ingredients on the drug release profile. The prototype formulation of micro pellets were prepared using the fluid bed coater (FBC) with the air pressure 2.0 bar and the spray rate 10-15ml/min. Temperature of bed is varied from 35°C to 50°C and inlet temperature is varied from 50°C to 70°C and the effect of various parameter were observed such as air pressure, inlet and outlet temperature of FBC, it is observed that at high pressure the pellets are breaking. For bed and inlet temperature it is observed that at low temperature lumps are occurring in the formulation and at 2.0 bar air pressure, inlet temperature 60°C and bed temperature of 40°C is reliable for solution flow rate 10-15ml/min. Concerning results of prototype preparation of Lansoprazole the micro pellets were prepared using HPMC E5 polymer as release retardant in three different concentration i.e. 40%, 50%, 60% with three different concentration 8%, 10%, 12% of NaOH and Acrycoat L30D solution was used for enteric coating. Formulated micro pellets showed delayed *in vitro* dissolution behavior, probably due to optimized concentration of polymer. The micro pellets drug was stable at room temperature, 25°C/60% RH, 30°C/65% RH and 40°C/75% RH as per ICH guidelines, after 3 months.

**Key Words**: Micropellets, Lansoprazole, HPMC E5, Acrycoat L30D, PEG 6000, Tween 80.

## INTRODUCTION

Gastroesophageal reflux disease or GERD occurs when the lower esophageal sphincter (LES) does not close properly and stomach contents leak back, or reflux, into the esophagus. The LES is a ring of muscle at the bottom of the esophagus that acts like a value between the esophagus and stomach. The esophagus carries food from the mouth to the stomach.

When refluxed stomach acid touches the lining of the esophagus, it causes a burning sensation in the chest or throat called heartburns. The fluid may even be tested in the back of the mouth, and this is called acid indigestion. Occasional heartburn is common but does not necessarily mean one has GERD. Heartburn that occurs more than twice a week may be considered GERD, and it can eventually lead to more serious health

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problems. Anyone, including infants, children and pregnant women, can have GERD.

Lansoprazole is one of the classes of proton pump inhibitors, which reduce gastric acidity, an important factor in healing acid-related disorders such as gastric ulcer, duodenal ulcer and reflux oesophagitis. It is used to treat gastro-oesophageal reflux disease, ulcers, acid-related dyspepsia and as an adjuvant in the eradication of *H. pylori*.[2,3,4]

Pellets are of great interest to the pharmaceutical industry for variety of reasons. Pelletized products not only offer flexibility in dosage form design and development, but are also utilized to improve safety and efficacy of bioactive agents. The focal intent of the present cram was to develop a stable, pharmaceutically equivalent, robust and delayed release micro pellet formulation of Lansoprazole.

## MATERIALS AND METHODS

### MATERIALS

Lansoprazole was obtained as gift sample from Active Pharmaceutical Ingredient, Sugar pellets, HPMC E5 and Poly vinyl pyrolidone from I.S.P Technologic Inc Texascity. PEG 6000 and Acry Coat L 30 D from Powder Rant Renidice Pvt. Ltd, Titanium Di Oxide from Rohadyc Chem Pvt. Ltd, Tween 80, from Bendale Chemicals, Iso-propyl Alcohol from Deepak Fertilizers and Petrocam Ltd. All other ingredients used were of analytical grade.

### METHODS

***Preparation of Lansoprazole micropellets***

The prototype micropellets of lansoprazole were prepared using PVPK30 to optimize the various parameters such as inlet temperature, outlet temperature and air pressure of Fluid Bed Coater. Then formulations of delayed release micropellets of lansoprazole were done using HPMC E5 as a release retardant in different concentrations (table 1).

***Drug Loading***

Sugar pellets were sieved through 30#40 and 33% of pellets was taken for drug loading from total batch size. Required quantity of drug was taken and dispersed in specified ml of NaOH solution and stirred for 10 minutes. The required quantity of HPMC E5 was taken and dispersed in specified ml of purified water and stirred for 10 minutes to obtain a clear solution. NaOH Solution was mixed with dispersed HPMC E5 solution with stirring. Pellets were loaded using dispersion both in to FBC bowl and coated

***Barrier coating***

Required quantity of Drug loaded pellets was taken for Barrier coating. Required quantity of HPMC E5 was taken and dissolved in specified ml of purified water and stirred until a clear solution was obtained and coating was done (table 2).

***Enteric coating***

Specified quantity of Barrier coated pellets were taken for Enteric coating. Required quantity of Acrycoat L30D solution, Talc, Titanium Dioxide, PEG 6000 and Tween 80 (Table 2)were taken and dispersed in specified ml of purified water and stirred for 10 minutes to obtain a clear solution. The prepared dispersion was mixed with Acrycoat L30D solutions with required quantity of NaOH solution for pH adjustment and coating was done.

***Evaluation of powder blend* and pellets**

The formulated powder blend were evaluated for compatibility, particle size shape analysis using Malvern particlesizer (MS 2000)[5], angle repose[6], hausner's ratio, compressibility index, bulk density, true density and Granule density[5], flow rate, Carr's Index.

***In-vitro Dissolution studies***

The release of drug from the developed formulations in the environment of gastrointestinal tract was determined using the USP XXIII dissolution apparatus II (Electro lab TDT – 08L). Capsules containing micro pellets equivalent to 30 mg of Lansoprazole in beaker containing 900 ml of 0.1N HCl of dissolution media maintained at 37 ± 0.5°C and 100 rpm. After 1 hour the medium was drained without losing the pellets and 900 ml of pre heated buffer solution of pH 6.8 added, study was further continued for 60 minutes at 75 rpm. Aliquot of samples were withdrawn at every 15 minutes each time which was replaced by the same amount of fresh medium. The samples were Centrifuge at 5000 rpm for 5 minutes of the above solution, and clear supernatant liquid was used. Correction factors for each aliquot were considered in calculation of release profile. Absorbance of sample after proper dilution was measured at 285 nm using HPLC Dionex (chromeleon) against blank. Concentration of drug was determined from the standard plots of the drug in buffer and the percentage drug release was calculated at each sampling time.

***Dissolution profile Comparisons (Using a Similarity Factor)***

A simple model independent approach uses a difference factor ($f_1$) and a similarity factor ($f_2$) to compare dissolution profiles. The difference factor ($f_1$) calculates the percent (%) difference between the two curves at each point and is a measurement to the relative error between the two curves:

$$f_1 = \{[\sum_{n=1} n \left| R_t - T_t \right|] / [\sum_{t=1} n R_t]\} * 100$$

Where *n* is the number of time point, $R_t$ is the dissolution value of the reference batch at time t, and $T_t$ is the dissolution value of the test batch at time t.

The similarity factor ($f_2$) is the logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) dissolution between the two curves.

$$f_2 = 50 \bullet \log \{[1+ (1/n) \sum_{t=1} n (R_t - T_t)^2]^{-0.5} \bullet 100\}$$

For the curves to be considered similar, $f_1$ values should be close to 0, and $f_2$ values should be close to 100. Generally, $f_1$ values up to (0-15) and $f_2$ values greater than 50 (50-100) ensures sameness or equivalence of the two

curves and thus, of the performance of the test and reference products. The comparative dissolution was performed using Lanzol 30mg[7].

***Gastric Resistance study***

The release of drug from the developed formulations in the environment of gastrointestinal tract was determined using the USP XXIII dissolution apparatus II (Electro lab TDT – 08L). Capsules containing micro pellets equivalent to 30 mg of Lansoprazole in beaker containing 900ml 0.1 HCl N of dissolution media maintained at 37 ± 0.5°C and 75 rpm. After 1 hour 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, 40ml of 0.1M NaOH was added and sonicator to dissolve. Further it was diluted up to 100 ml with 0.1M NaOH. About 15 ml of solution was centrifuged for 5 minutes. 5 ml of the clear supernatant liquid was diluted to 50 ml with mobile phase. Absorbance of sample after proper dilution was measured at 285 nm using HPLC Dionex (chromeleon) against blank.

***Drug Content***

Equivalent weights to equivalent to 30mg of Lansoprazole into a dry 100 ml volumetric flask added about 50 ml of 0.1 M NaOH and sonicate to dissolve. The volume was make up to the mark with 0.1 M sodium hydroxide and mix. 20 to 30 ml of solution was transferred into dry stoppered test-tube and it was centrifuge at 5000rpm for 5 minutes. Samples were analyzed using HPLC Dionex (chromeleon) at a wavelength of 285nm. The drug content was determined by diluting 5 ml of the supernatant solution to 50ml with mobile phase.

***Accelerated stability studies***

Formulation were stored at various temperature *viz.* 25°C/60% RH, 30°C/65% RH and 40°C/75% RH as per ICH guidelines and various physicochemical parameter (appearance, percentage drug content and release profile) were monitored periodically for 3 months[8].

## RESULTS AND DISCUSSION

Lansoprazole micro pellets formulated, using HPMC E5 as release retardant in various concentration with an enteric coating. Lansoprazole micro Pellets were prepared by applying optimized pressure and temperature in fluid bed coater technique. Lansoprazole meets all the ideal characteristics to formulate in the form of oral drug delivery system.

Under Preformulation study, FTIR analysis between the drug and enteric polymer mixture showed no unaccountable extra peaks, which confirms the absence of chemical interaction between the drug and polymer.

***Physical characterization***

Powder blend of Lansoprazole and micro pellets were evaluated for various physiochemical parameters.

The organoleptic properties were complied with the British Pharmacopeia specification. Physical properties such as particle size analysis, bulk density of raw material powder, Melting point. Solution properties solubility evaluated, results were complied with the pharmacopeia specification. Loss on drying was within the British Pharmacopeia limit and the result of angle of repose of powder showed the poor flow properties. Angle of repose and flow rates of the different formulations were compared with bulk drug, Lansoprazole, which shows that after pellets formulation flow properties and flow rate were excellent. Assay of Lansoprazole was carried out using HPLC and it was found to be 99.6% (figure 5). Technological characterizations of formulated Lansoprazole powder blend and micropellets formulation are shown in (table 3).

***In Vitro Dissolution Studies***

The dissolution rate studies for each of the formulations were performed in order to assess the effect of increase in surfactant concentration on release profile. In dissolution studies, 900ml solution of 0.1N HCl was taken for one hour and followed by 900ml phosphate buffer pH 6.8 to mimic the cumulative release of drug in stomach. Result of *in vitro* dissolution rate studies are shown in (table 4) (figure 1).

***Dissolution profile Comparisons (Similarity Factor)***

The dissolution comparisons by model independent approach using a similarity factor $f_1$ is found to be 2.18 and $f_2$ found 86.53 (table 5) (figure 2).

***Gastric Resistance study***

Acid resistances study shows that the optimized formulation F9 is more stable in the acidic media i.e 99.36% of drug was released in 60 minutes. Result of acid resistances studies are correlated in (table 4) (figure 3).

***Accelerated stability studies***

The selected formulations were subjected for accelerated stability studies as per the ICH guidelines. There were no changes in appearances and percentage drug content of pellets stored at different temperature for drug remaining *vs.* time at 25°C/60% RH, 30°C/65% RH and 40°C/75% RH. All the parameter were within the limit after 90 days.

## CONCLUSION

The study was undertaken with an aim to develop delayed release micro pellet dosage form for Lansoprazole, which is a benzimidazole anti ulcer agent and is one of the most widely used drug for treating mild and severe ulcers. Based on the Drug-Excipient compatibility data and prototype formulations, the formula that found to be giving the desired drug release pattern was considered as the optimized formulation and further studies were conducted on this formulation F9 to have a detailed study over that formulation. By the observations made, it was concluded that the formulation F9 shows delayed release profile and it was within the USP limits, and also this formulation done by FBC process which is a sophisticated method. Then this formulation was compared with marketed product by an *in vitro* study, which definitely improves patient's compliances and reduces the gastric side effect..

**Table 1.** ***Formulation of Lansoprazole micropellets***

| **Ingredients( in percent )** | **Formulation code** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Prototype formulation with PVP- K 30** | | | **Formulation with HPMC-E5** | | | | | | | | |
| | **FP1** | **FP2** | **FP3** | **F1** | **F2** | **F3** | **F4** | **F5** | **F6** | **F7** | **F8** | **F9** |
| Lansoprazole % based on batch size | 8.5 | 8.5 | 8.5 | 8.5 | 8.5 | 8.5 | 8.5 | 8.5 | 8.5 | 8.5 | 8.5 | 8.5 |
| PVP K 30 to the drug | 40 | 50 | 60 | - | - | - | - | - | - | - | - | - |
| HPMC E-5 to the drug | - | - | - | 40 | 40 | 40 | 50 | 50 | 50 | 60 | 60 | 60 |
| NaOH to the drug | 8 | 8 | 8 | 8 | 10 | 12 | 8 | 10 | 12 | 8 | 10 | 12 |
| Sugar spheres (30#40) to the batch size | 33 | 33 | 33 | 33 | 33 | 33 | 33 | 33 | 33 | 33 | 33 | 33 |
| D.M.Water | Qs. | Qs. | Qs. | Qs. | Qs. | Qs. | Qs. | Qs. | Qs. | Qs. | Qs. | Qs. |

**Table 2.*Technological characterization of coating formula on optimized formulation F9***

| **Prototype formulation with PVP- K 30** | | **Formulation with HPMC-E5** | |
|---|---|---|---|
| ***Barrier coating formula*** | | | |
| **Ingredients** | **Qty.** | **Ingredients** | **Qty.** |
| HPMC E5 | 12 % of drug loaded pellets. | HPMC E5 | 12 % of drug loaded pellets. |
| Purified water | 12% × 16 Portion | Purified water | 12% × 16 Portion |
| ***Enteric coating formula*** | | | |
| Acry coat L 30 D Solution | 60% of barrier coated pellets × 3.33 | Acry coat L 30 D Solution | 60% of barrier coated pellets × 3.33 |
| Talc | 5% of Acry coat L 30 D solution | Talc | 5% of Acry coat L 30 D solution |
| Titanium Dioxide | 2% of Acry coat L 30 D solution | Titanium Dioxide | 2% of Acry coat L 30 D solution |
| PEG 6000 | 3.6% of Acry coat L 30 D solution | PEG 6000 | 3.6% of Acry coat L 30 D solution |
| Tween 80 | 0.5% of Acry coat L 30 D solution | Tween 80 | 0.5% of Acry coat L 30 D solution |
| Sodium Hydroxide | 0.2% of Acry coat L 30 D solution | Sodium Hydroxide | 0.2% of Acry coat L 30 D solution |
| Purified Water | Equal to Acry Coat L 30 D solution. | Purified Water | Equal to Acry Coat L 30 D solution. |

**Table 3.** ***Technological characterization of formulated Lansoprazole powder blend and micropellets formulation****

| Parameters | Lansoprazole | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|---|
| **Angle of repose*** | 39.11±0.65 | 24.23±0.02 | 24.48±0.04 | 25.06±1.06 | 23.93±0.19 | 25.18±0.33 | 25.14±0.14 | 25.92±0.14 | 24.72±0.15 | 23.31±0.04 |
| **Flow rate gm/sec*** | - | 8.2±0.24 | 7.9±0.19 | 8.7±0.11 | 6.7±0.27 | 8.4±0.32 | 8.4±0.29 | 9.1±0.17 | 8.7±0.11 | 7.7±0.28 |
| **Hausner's ratio** | 1.43 | 1.07 | 1.07 | 1.07 | 1.06 | 1.04 | 1.04 | 1.08 | 1.04 | 1.05 |
| **Carr's Index** | - | 5.47 | 5.71 | 4.38 | 4.96 | 5.21 | 5.47 | 5.39 | 5.11 | 4.96 |
| **Bulk density (gm/ml)*** | 0.4065±0.02 | 0.923± 0.01 | 0.937± 0.01 | 0.921±0.03 | 0.934±0.01 | 0.915±0.01 | 0.952±0.03 | 0.947±0.01 | 0.928±0.04 | 0.938±0.06 |
| **Tapped density (gm/ml)*** | 0.5813±0.03 | 0.989±0.01 | 1.004±0.01 | 0.988±0.04 | 0.991±0.02 | 0.959±0.03 | 0.999±0.06 | 1.028±0.01 | 0.972±0.03 | 0.987±0.05 |
| **Granules density*** | - | 1.93±0.04 | 2.01±0.02 | 1.97±0.08 | 2.08±0.03 | 2.00±0.05 | 1.87±0.03 | 2.29±0.02 | 2.05±0.01 | 1.97±0.02 |
| **Loss on drying (%)** | 0.19 | 2.16 | 2.36 | 2.86 | 2.71 | 2.05 | 2.36 | 2.03 | 2.48 | 2.61 |
| **Friability%** | - | 0.07 | 0.125 | 0.21 | 0.114 | 0.087 | 0.089 | 0.075 | 0.097 | 0.084 |
| **Assay (%)** | 99.97 | 84.07 | 84.27 | 85.15 | 90.62 | 86.01 | 91.72 | 96.15 | 98.47 | 99.86 |

***All values are mean ± S.D. for n=3**

**Table 4.** ***In vitro Release Profile of Percentage Cumulative Drug Release from various formulations*** **and Acid** ***Resistance Dissolution Data****

| Time in minutes | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|
| ***Dissolution profile of Lansoprazole 30mg capsules*** | | | | | | | | | |
| 0 | 0.00 | 0.00 | 0.00 | 0.00 | 0.0 | 0.00 | 0.00 | 0.00 | 0.00 |
| 15 | 45.74±0.55 | 48.35±1.06 | 50.32±1.10 | 53.07±1.57 | 56.28±0.91 | 54.69±0.25 | 58.65±0.11 | 62.87±0.64 | 63.92±1.49 |
| 30 | 58.36±0.22 | 52.87±1.12 | 55.18±1.81 | 62.81±0.67 | 64.16±1.15 | 67.48±0.93 | 64.87±1.57 | 71.86±0.46 | 76.43±0.57 |
| 45 | 66.54±0.26 | 68.74±0.69 | 65.67±0.58 | 68.49±1.81 | 71.33±1.08 | 73.61±0.81 | 75.46±0.61 | 78.26±0.74 | 83.88±1.61 |
| 60 | 72.18±1.08 | 73.28±1.62 | 75.48±1.88 | 77.52±1.20 | 79.65±1.23 | 77.21±0.23 | 81.52±1.07 | 85.68±0.61 | 89.24±1.99 |
| ***Acid Resistance Dissolution Data*** | | | | | | | | | |
| 0 | 0.00 | 0.00 | 0.00 | 0.00 | 0.0 | 0.00 | 0.00 | 0.00 | 0.00 |
| 60 | 89.68±0.55 | 87.48±1.81 | 88.25±0.90 | 92.33±0.69 | 87.68±1.02 | 91.25±1.50 | 95.56±1.05 | 97.00±0.85 | 99.37±1.25 |

***All values are mean ± S.D. for n=3**

**Table 5.** ***Comparative Dissolution Profile of F9 with Reference***

| Time in minutes | F – 9 | Reference ( Lanzol 30mg ) |
|---|---|---|
| 0 | 0 | 0 |
| 15 | 63.92±1.49 | 62.14±1.01 |
| 30 | 76.43±0.57 | 74.27±0.96 |
| 45 | 83.88±1.61 | 83.27±1.10 |
| 60 | 89.24±1.99 | 87.98±0.99 |

**Figure 1:** ***Comparative dissolution profiles of formulations F1-F9***

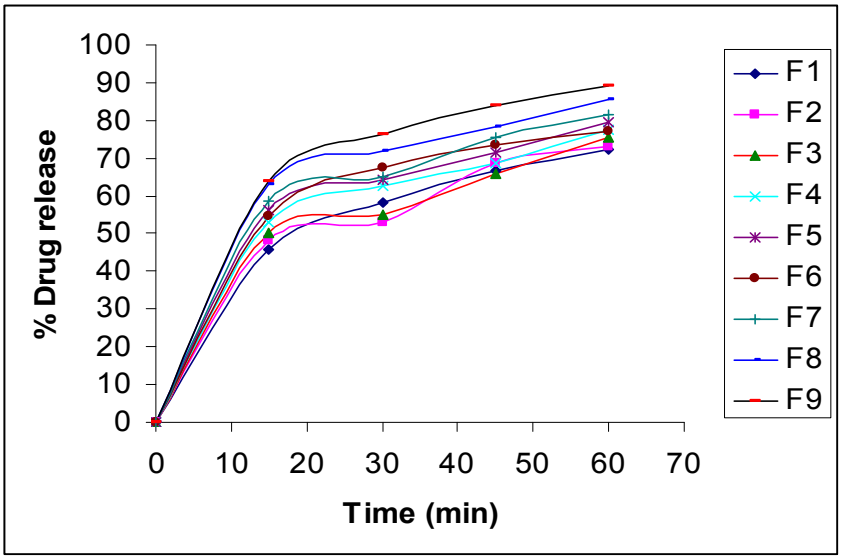



**Figure 2:** ***Comparative Dissolution Profile of F9 with Reference***

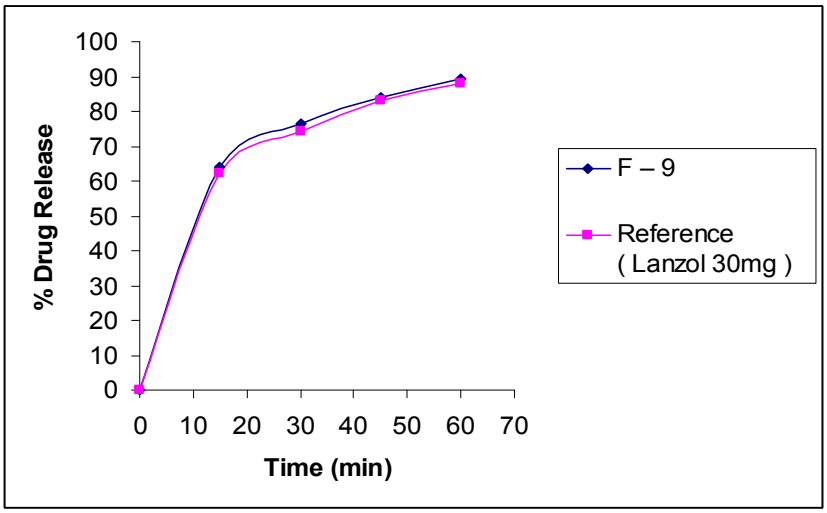


**Figure 3:** ***Acid resistant dissolution data of lansoprazole micropellets in pH 1.2***

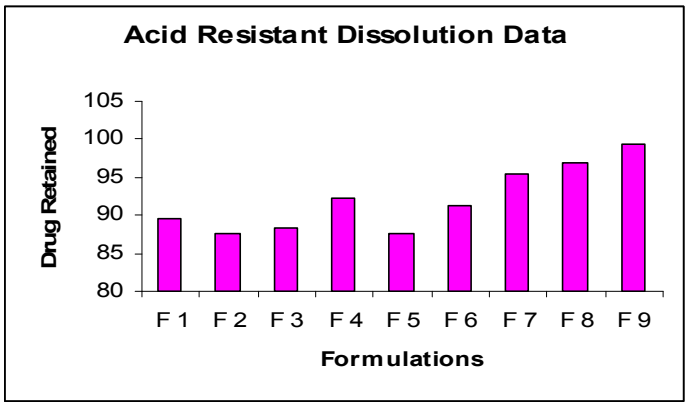



**Figure 4:** ***Drug content uniformity of various formulations***

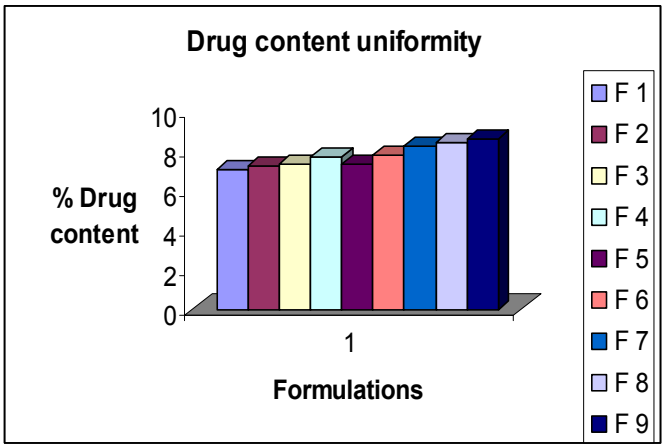



**Figure 5:***: FTIR Spectrum of Lansoprazole*

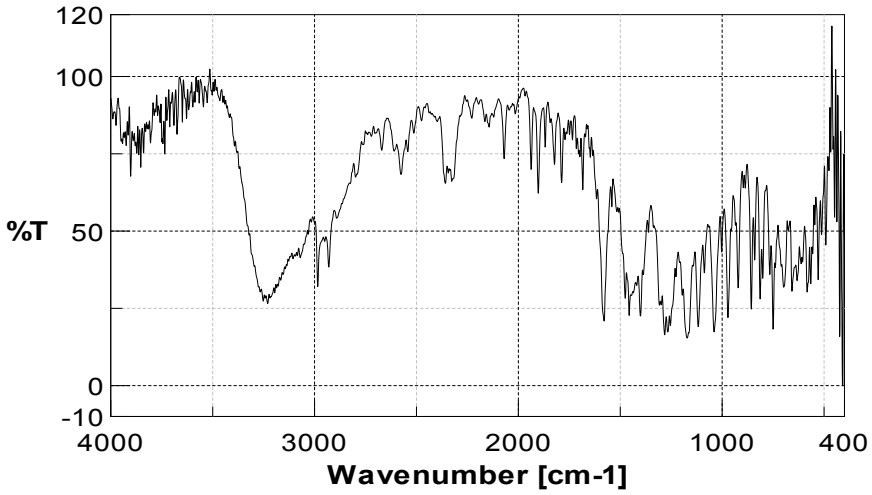



**Figure 6:** ***FTIR Spectrum Lansoprazole with PVP K-30***

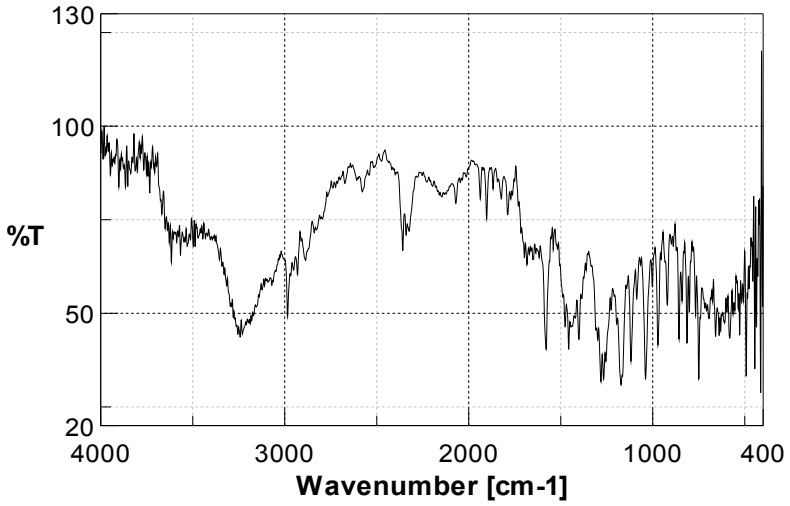



**Figure 7:** ***FTIR Spectrum Lansoprazole with HPMC-E-5***

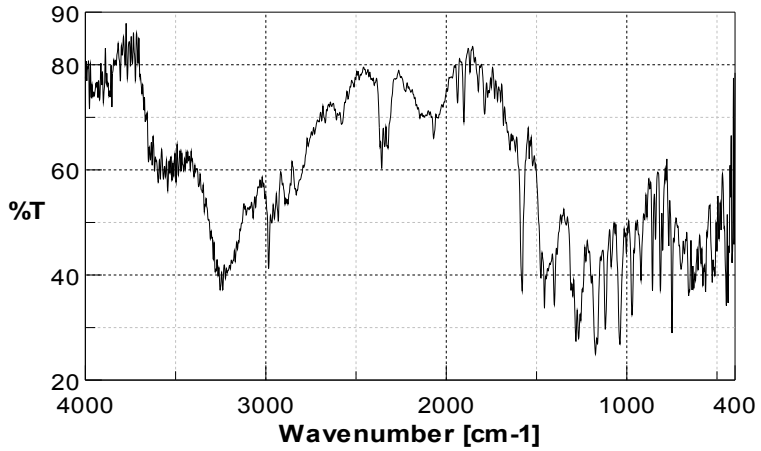
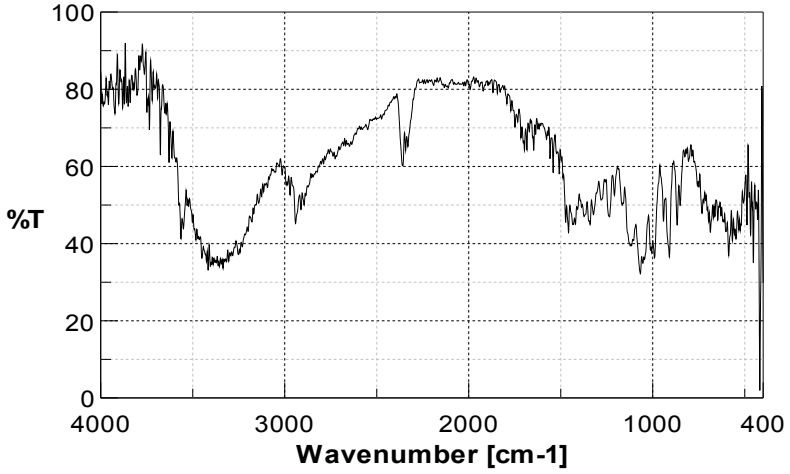



**Figure 8:** ***FTIR Spectrum Lansoprazole micro pellets 8.5% w/w***



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