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# FORMULATION, DEVELOPMENT AND EVALUATION OF BUFFER ESOMEPRAZOLE TABLET IN TABLET PREPARATION

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## ABSTRACT

Esomeprazole is the S-isomer of omeprazole, which is a mixture of the S- and R- isomers. The stability of Esomeprazole magnesium is a function of pH; it rapidly degrades in acidic media, but it has acceptable stability under alkaline conditions. As the API is acid Habile, so the main strategy was to develop a formulation giving protection to API as well as safe and effective release so as to impart its action in an effective manner. So first of all conventional formulations were designed having drug and buffer part compressed together (Tablet in Tablet), along with alkalizing agent. The purpose of the research work as the esomeprazole is acid Habile, so the main strategy was to develop a formulation giving protection to API as well as safe and effective release so as to impart its action in an effective manner. So first of all conventional formulations were designed having drug and buffer part compressed together (Tablet in Tablet), along with alkalizing agent. The formulation is designed as a way to have release as well as, to give protection to drug part against acid environment of stomach, for that tablet in tablet strategy was followed in such a way that buffer part of final tablet provide protection to drug part by mechanism of raising pH as well as by maintaining that pH range for a period of sufficient time so that total drug from inner tablet is released and absorb from that pH. The prepared batches of tablets were evaluated for hardness, friability, drug content, wetting time, dispersion time, disintegration time and dissolution studies. Based on tested for *in-vitro* drug release pattern (in 0.1N HCL) and short term stability studies. Among the promising formulations, the formulation F6 emerged as the overall best formulation based on drug release characteristic.

***Key words***: Tablet in tablet, Esomeprazole, *in-vitro* drug release.

## INTRODUCTION:

The oral route of drug administration is the most common and preferred method of delivery due to convenience and ease of ingestion. From a patient's perspective, swallowing a dosage form is a familiar means of taking medication. As a result, patient compliance and hence drug treatment is typically more effective with orally administered medications as compared with other routes of administration (Bagman *et.al*.2013). The concept of pH does not apply to solids, the terms microenvironmental pH or surface pH have been used in conjunction with solid formulations (Badawy *et.al.* 1999). Those terms have been loosely used to describe hydrogen ion activity in non-crystalline regions such as sorbed water layers or water-plasticized amorphous domains (Glombitza et.al. 1994, Glombitza and Schmidt, 1994). The microenvironmental pH has been implicated as a factor influencing drug degradation of solid dosage forms. Microenvironmental pH also affects dissolution behavior and hence bioavailability of many compounds, especially weak bases. The concept of microenvironmental pH, however, is not well defined and there are no well-established techniques available to measure it (Zinchuck et al. 2005).

The objective can be designed in such a manner that a tablet of esomoprazole will be manufactured by using direct compression/dry granulation method, than after tablet compression, film coating of same tablet, then will be further compressed with the buffer granules contains (tablet in tablet). After administration of the tablet in tablet, it will be disintegrate in the stomach immediately.

## MATERIAL AND METHODS:

API (Esomeprazole magnesium trihydrate) and other necessary excipients were kindly provided by Torrent Pharma Ltd, Ahmedabad, Gujrat, India. All the reagents and solvents used in the experimentation were of AR grade unless otherwise specified.

### Methods:

### Formulation of Esomoprazole Inercoat tablet:

Immediate release tablets of Esomoprazole were prepared by wet granulation method according to the formula given in Table 1. Esomoprazole, microcrystalline cellulose and crosspovidone sifted through sieve No. 40 and thoroughly mixed in a Rapid Mixer Granulator (RMG) for 10 min. PVP K30 dissolved in sufficient quantity of IPA, and used as a binder solution. Wet granules were dried in fluid bed dryer (FBD) at 60-65°C till a LOD (Loss of drying) of dried granules obtained not more than 2% w/w. Dried granules were passed through sieve No.24. The dried granules were lubricated for 2 min with Magnesium Stearate and talc. The lubricated granules were then compressed in to tablets on an 8 station rotary machine to get a tablet of 160 mg weight.

**Formulation of Outer coat tablet of Esomoprazole:**

After punching of inner coat, microcrystalline cellulose, cross carmellose sodium, crosspovidone, sifted through sieve No. 40 and thoroughly mixed in a Rapid Mixer Granulator (RMG) for 10 min according to the formula given in Table 2. PVP K30 dissolved in sufficient quantity of IPA, and used as a binder solution. Wet granules were dried in fluid bed dryer (FBD) at 60-650C till a LOD (Loss of drying) of dried granules obtained not more than 2% w/w. Dried granules were passed through sieve No.24. The dried granules were lubricated for 2 min with Magnesium Stearate and talc. The lubricated granules were then compressed in to tablets on an 8 station rotary machine to get a tablet of 1500 mg weight.

**Table 1: Formulation of Inner coat tablet of Esomoprazole:**

| **Ingredients** | F1 | F2 | F3 | F4 | F5 | F6 |
|---|---|---|---|---|---|---|
| Esomeprazole Magnesium | 44.60 | 44.60 | 44.60 | 44.60 | 44.60 | 44.60 |
| Microcrystalline Cellulose (PH-102) IP | 111.39 | 109.60 | 107.85 | 111.39 | 109.60 | 107.85 |
| Cross Carmellose Sodium | -- | -- | -- | 3.0 | 5.0 | 7.0 |
| Crospovidone XL -10 | 3.0 | 5.0 | 7.0 | -- | -- | -- |
| Polyvinyl pyrrolidone (K-30) | 0.13 | 0.13 | 0.13 | 0.13 | 0.13 | 0.13 |
| IPA | q.s. | q.s. | q.s. | q.s. | q.s. | q.s. |
| Talc | 0.17 | 0.17 | 0.17 | 0.17 | 0.17 | 0.17 |
| Magnesium stearate | 0.25 | 0.25 | 0.25 | 0.25 | 0.25 | 0.25 |
| Total Weight | 160.0 | 160.0 | 160.0 | 160.0 | 160.0 | 160.0 |

**Table 2: Formulation of outer coat tablet of Esomoprazole:**

| **Ingredients** | F1 | F2 | F3 | F4 | F5 | F6 |
|---|---|---|---|---|---|---|
| Microcrystalline Cellulose (PH-102) IP | 170.00 | 170.00 | 170.00 | 170.00 | 170.00 | 170.00 |
| Peppermint flavor / Cardamom flavor | 7.000 | 7.000 | 7.000 | 7.000 | 7.000 | 7.000 |
| Sodium Bicarbonate (Crystalline powder) | 1100.00 | 1100.00 | 1100.00 | 1100.00 | 1100.00 | 1100.00 |
| Colloidal silicon dioxide(Aerosil) | 3.00 | 3.00 | 3.00 | 3.00 | 3.00 | 3.00 |
| Crospovidone XL -10 | 21.00 | 21.00 | 21.00 | 21.00 | 21.00 | 21.00 |
| Polyvinyl pyrrolidone (K-30) | 13.00 | 13.00 | 13.00 | 13.00 | 13.00 | 13.00 |
| IPA | Qs | Qs | Qs | Qs | Qs | Qs |
| Talc | 13.00 | 13.00 | 13.00 | 13.00 | 13.00 | 13.00 |
| Magnesium stearate | 3.00 | 3.00 | 3.00 | 3.00 | 3.00 | 3.00 |

**EVALUATION OF TABLET:**

**Evaluation of Powder Blend [6-9]**

**Bulk density:**

It is a ratio of mass of powder to bulk volume. The bulk density depends on particle size distribution, shape and cohesiveness of particles. Accurately weighed quantity of powder was carefully poured in to graduated measuring cylinder through large funnel and volume was measured, which is called initial bulk volume (Ohwoavworhua et. al. 2004). It is expressed in gm/ml and is given by the formula

$$\textbf{Bulk density} = M/Vo$$

Where, M = mass of the powder

Vo = bulk volume of the powder

**Tapped density:**

Ten gram of powder was introduced into a clean, dry 100 ml measuring cylinder. The cylinder was then tapped 100 times from a constant height and the tapped volume was read (Bultman et.al. 2002). It is expressed in gm/ml and is given by

$$\textbf{Tapped density} = M/V_t$$

Where, M = mass of the powder

$V_t$ = final tapping volume of the powder

**Angle of repose (θ)**

It is defined as the maximum angle possible between the surface of the pile of the powder and

the horizontal plane. Fixed funnel method was used. A funnel was fixed with its tip at a given height 'h, above a flat horizontal surface to which a graph paper was placed. Powder was carefully poured through a funnel till the apex of the conical pile just touches the tip of the funnel (Mashadi et.al. 1987). The angle of repose was then calculated using following equation

**Angle of repose (Ø) = tan-1(h/r)**

Where, h=height of the pile

r = radius of the pile

**Compressibility index (Carr's index)**

Compressibility index is used as an important parameter to determine the flow behavior of the Powder. It is indirectly related to the relative flow property rate, cohesiveness and particle size. It is Simple, fast and popular method for predicting flow characteristics. Carr's index can be represented by Equation

$$\text{Carr's Compressibility Index (\%)} = \frac{\text{Tapped density - bulk density}}{\text{Tapped density}} \times 100$$

**Hausner's ratio**

Hausner's ratio is used to predict the flow ability of the powders (Hancock et.al. 2000). This method is similar to compressibility index. Hausner's ratio can be represented by Equation

$$\text{Hausner's Ratio} = \frac{\text{Tapped density}}{\text{Bulk Density}}$$

**EVALUATION OF TABLETS [10-13]**

All the tablets were evaluated for different parameters as thickness, hardness, friability, uniformity of weight, disintegration time, drug content and in vitro dissolution study (Lachman et.al 1987, Liberman et.al 1989, Shoukri et.al 2009, Tejakrishna et. al. 2013).

**Dimensional Analysis** The thickness and diameter of tablets was determined using Vernier Caliper. Twenty tablets from each batch were used and average values were calculated.

**Hardness**

The Monsanto hardness tester was used to determine the tablet hardness. The tablet was held between affixed and moving jaw. Scale was adjusted to zero; load was gradually increased until the tablet fractured. The value of the load at that point gives a measure of the hardness of the tablet. It is expressed in kg/cm$^2$. For each formulation, the hardness of six tablets was determined and average value was calculated.

**Weight variation**

Randomly selected twenty tablets were weighed individually and together in a single pan balance. The average weight was noted and standard deviation calculated. The tablets pass the test if not more than two tablets fall outside the percentage limit and none of the tablet differs by more than double percentage limit.

$$\mathbf{PD = [(W_{avg} - W_{initial}) / (W_{avg})] \times 100}$$

Where, PD = Percentage deviation,

$W_{avg}$ = Average weight of tablet,

$W_{initial}$ = Individual weight of tablet

**Drug content**

Tablets were crushed and the powder equivalent to 100mg of drug were accurately weighed and transferred to 50 ml volumetric flask. To this flask, sufficient amount of distilled water was added to dissolve the tablets completely. Then, the volume of flask was made up to the mark with same solvent. From this solution, 1ml of the sample was pipette out and transferred to 10 ml volumetric flask. The volume in the second flask was made up to the mark with distilled water. From this 0.6ml, 0.8ml, and 1ml samples were withdrawn and volume was made up to 10ml to maintain concentration within the beer's range. This final diluted solution was estimated UV spectrophotometrically at 298 nm.

**Friability**

Twenty tablets samples were weighed accurately and placed in friabilator (Roche Friabilator). After the given specification (4 min at 25 rpm), loose dust was removed from the tablets. Finally tablets were weighed. The loss in weight indicates the ability of the tablets to withstand this type of wear. The % friability was then calculated by

**% Friability = (Loss in weight / Initial weight) × 100**

**Disintegration test**

Disintegration is evaluated to ensure that the drug substance is fully available for dissolution and absorption from the gastrointestinal tract. Disintegration test was carried out using tablet disintegration test apparatus (EI Instrument, India) using distilled water without disk at room temperature (37±2°C).

***In vitro* Drug release studies**

*In vitro* drug release studies were carried out in 900 ml of 0.1N HCl for the first 2 h using a USP XXII type 1 dissolution apparatus (Electrolab TDT-08L) at 60 rpm and 37 ± 0.5 °C. At predetermined time intervals during the dissolution test, samples (10 ml) were withdrawn for assay and replaced with equivalent volume of fresh medium to maintain conditions. All dissolution studies were performed in triplicate. The samples were filtered, diluted appropriately and then analyzed spectrophotometrically (Systronics, India) for esomeprazole at 298 nm.

**Stability Study:**

Stability studies were conducted on buffer tablets of select batch to assess their stability with respect to their Hardness, weight variation and release characteristics after storing at 25˚C under 60% relative humidity (RH) and 40˚C under 75% RH for 3 months. At an interval of 7 days, the tablets were visually examined for hardness, weight

variation and *in vitro* dissolution test (Bansal *et.al*. 2013)

**Result and Discussion:**

**Evaluation of Esomeprazole Granules:** Esomeprazole powder and the prepared granules were evaluated for angle of repose, poured density, tapped density and compressibility index which was shown in Table 3. The angle of repose of pure Esomeprazole powder could not be measured because the powder was too cohesive to flow through the funnel, where as the value of prepared granules ranged from 26-31. The housner,s ratio for granules ranged from 1.18-1.40, which shows good flow property as a result of increase in particle size owing to granulation. Tapped density of the granules was decreased due to increase in the particle size compared with the pure drug. The % compressibility value for pure Esomeprazole was found to be 15.96-25.47, which shows that the pure drug have very poor flowability

**Table 3: Evaluation of Pre compressed Powder Blend**

| Formulation Code | Bulk Density (gm/ml) | Tapped Density (gm/ml) | Angle of Repose (θ) | Carr's Compressibility Index | Hausner's Ratio |
|---|---|---|---|---|---|
| **F1** | 0.36±0.021 | 0.46±0.043 | 28 ±0.424 | 21.14±0.53 | 1.26±0.68 |
| **F2** | 0.32±0.030 | 0.45±0.048 | 31 ±0.413 | 28.95±0.63 | 1.40±0.67 |
| **F3** | 0.35±0.032 | 0.45±0.042 | 29 ±0.436 | 22.56±0.63 | 1.29±0.68 |
| **F4** | 0.35±0.024 | 0.48±0.041 | 26 ±0.301 | 25.47±0.62 | 1.34±0.63 |
| **F5** | 0.43±0.022 | 0.53±0.042 | 28 ±0.536 | 18.17±0.58 | 1.22±0.58 |
| **F6** | 0.46±0.037 | 0.55±0.046 | 27 ±0.465 | 15.96±0.61 | 1.18±0.67 |

All values are presented as Mean ±S.D.

**Evaluation of Esomeprazole Tablet in Tablet:**

**Weight Variation:**

The weight variation was prominent in the formulations with more lactose because of poor flow Properties of the powder mixture. It ranged from 1480 mg to 1508 mg with very high values of standard deviation. On increasing microcrystalline cellulose the weight variation was significantly reduced. The results are shown in table no. 4. All formulations pass the weight variation test.

**Thickness:**

The tablets from 4.21-4.81mm in thickness with minimum standard deviation values, it assumed that the tablets show uniformity in thickness. The results are given in Table 4.

**Hardness:**

The hardness of the tablets was found to be 5.31 - 6.07 kg/cm$^2$. The hardness of tablet varied although compression force was constant. The results are given in Table 4.

**Friability:**

The friability of the tablets was found to be 0.40-0.58%. The results are given in Table 4

**Drug Content:**

Drug content in the tablets was the limit of 97.61-98.83 %. The results are given in Table 4.

**Drug release:**

Comparative cumulative percentage drug release data of all formulations are given in table no. 5. Dissolution profiles of formulations F1 to F6 are shown in Figure 1**.** Drug release for different batches was found to be 91.69 to 95.96 within 45 minute. The maximum drug release was observed in F6 among all formulations in 45 minute.

**Table 4: Evaluation of Buffer Tablets of Eosmoprazole**

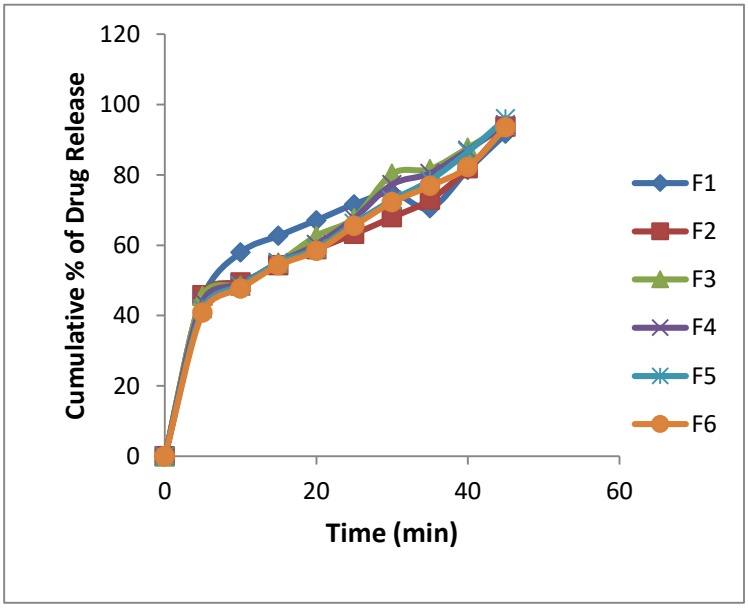
| Formulation Code | Hardness (kg/cm2) | Friability (%) | Weight Variation (mg) | Content uniformity (%) | Thickness (cm) | Disintegration Time (min) |
|---|---|---|---|---|---|---|
| **F1** | 5.46±0.1634 | 0.58±0.0053 | 1504±1.8593 | 97.61±0.0572 | 4.81±0.0753 | 14.31±0.3993 |
| **F2** | 5.40±0.1852 | 0.40±0.0148 | 1507±1.3376 | 98.11±0.0489 | 4.56±0.0582 | 13.46±0.4521 |
| **F3** | 5.53±0.2587 | 0.44±0.0061 | 1480±1.3497 | 98.23±0.0826 | 4.58±0.0891 | 14.12±0.4812 |
| **F4** | 5.31±0.8361 | 0.47±0.0085 | 1508±0.3993 | 99.38±0.0419 | 4.61±0.0189 | 13.62±0.5839 |
| **F5** | 6.07±0.0649 | 0.43±0.0056 | 1494±0.3798 | 98.83±0.0629 | 4.21±0.0380 | 13.81±0.3653 |
| **F6** | 5.83±0.1569 | 0.42±0.0029 | 1504±0.3255 | 98.58±0.0583 | 4.88±0.0310 | 14.33±0.5822 |

**Table 5: Comparative *In vitro* % drug release profiles of formulations (F1-F6)**

| Time (Min) | Cumulative % of Drug release | | | | | |
|---|---|---|---|---|---|---|
| | **F1** | **F2** | **F3** | **F4** | **F5** | **F6** |
| 0 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |
| 5 | 44.93 | 45.79 | 45.63 | 44.0 | 40.90 | 41.91 |
| 10 | 57.16 | 49.40 | 48.54 | 48.84 | 47.72 | 48.43 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 15 | 62.68 | 54.37 | 55.06 | 55.04 | 54.30 | 55.01 |
| 20 | 67.09 | 58.86 | 62.64 | 60.22 | 58.38 | 59.03 |
| 25 | 71.62 | 63.23 | 67.74 | 67.62 | 65.53 | 66.26 |
| 30 | 74.87 | 67.94 | 80.34 | 77.27 | 72.21 | 72.80 |
| 35 | 70.54 | 72.94 | 81.67 | 80.43 | 76.86 | 78.46 |
| 40 | 81.45 | 81.86 | 87.68 | 87.02 | 82.25 | 86.59 |
| 45 | 91.69 | 93.73 | 94.24 | 94.30 | 93.52 | 95.96 |

**Fig 1: *Invitro* Drug Release of various Esomoprazole buffer tablet formulations.**




**Stability Study:**

Twenty tablets of optimized formulation (F6) were placed in Petridish. Which was kept in desiccators containing calcium chloride (desiccant) at room temperature for one day. Then the tablets were weighted and placed in humidity chamber, which was maintained at $25^0$C fewer than 60% relative humidity (RH) and 40˚C under 75% RH for 1 month.

Tablets were evaluated for weight variation, hardness and in-vitro dissolution at each predetermined intervals (after 1,2,3,4 weeks).

**Table 6: CHANGE IN WEIGHT OF OPTIMIZED FORMULATIONS DURING STABILITY STUDY**

| Product code | Temperature | Increase in weight (mg) of the Optimized Formulation | | |
|---|---|---|---|---|
| | | After 2 weeks | After 3 weeks | After 4 weeks |
| F6 | $25^0$c | 0.51 | 0.85 | 1.13 |
| | $40^0$c | 0.63 | 0.93 | 1.33 |

**Table 7: CHANGE IN HARDNESS (Kg/Cm2) OF OPTIMIZED FORMULATIONS DURING STABILITY STUDY**

| Product code | Temperature | Change in Hardness (Kg/Cm2) of the Optimized Formulation | | |
|---|---|---|---|---|
| | | At 2 weeks | At 3 weeks | At 4 weeks |
| F6 | $25^0$c | 4.4 | 3.8 | 3.7 |
| | $40^0$c | 4.8 | 4.3 | 4.0 |

**Table 8: CHANGE IN IN-VITRO DRUG RELEASE PROFILE OF OPTIMIZED FORMULATION DURING STABILITY STUDY**

| Product code | Temperature | In-vitro % Drug release profile | | |
|---|---|---|---|---|
| | | At 2 weeks | At 3weeks | At 4 weeks |
| F6 | $25^0$c | 93.58 | 92.69 | 91.29 |
| | $40^0$c | 94.58 | 93.76 | 92.32 |

## CONCLUSION

All formulations were found to be satisfactory when evaluated for thickness, weight uniformity, hardness, friability, drug content uniformity, disintegration time and *in-vitro* drug release. The tablet disintegration time was less than one minute for all the tablet formulations. The *in vitro* drug release in optimized formulation F6 was found to be 95.96 % in 45 min. The optimized formulation F6 also showed satisfactory hardness (5.83±0.1569 kg/cm2), friability (0.42±0.0029), drug content (98.58±0.0583), weight variation (1504±0.3255 mg), and disintegration time (14.33±0.5822 minutes) and stability.

**Reference:**

Badawy SIF, Williams RC, Gilbert D. Effect of different acids on solid state stability of an ester prodrug of a IIb/IIIa antagonist. Pharm Dev Technol. 1999;4: 325-331.

Bagman UR, Jade PS, Linked AS, Uttar war SG. Formulation and *in-vitro* evaluation of immediate release tablet of fexofenadine hydrochloride, Ameriacal journal of pharmatech research, 2013; 3(3): 635-643.

Bansal M, Bansal S, Garg G. Formulation and Evaluation of Immediate Release Tablets of Zaltoprofen, Sch. Acad. J. Pharm., 2013; 2(5):398-405.

Bultman JM; Multiple Compaction of Microcrystalline Cellulose in a Roller Compactor. Eur. J. Pharm. Biopharm., 2002; 54: 59–64.

Glombitza BW, Oelkrug D, Schmidt PC. Surface acidity of solid pharmaceutical excipients. Part 1. Determination of the surface acidity. Eur J Pharm Biopharm. 1994;4: 289-293.

Glombitza BW, Schmidt PC. Surface acidity of solid pharmaceutical excipients. Part 2. Effect of the surface acidity on the decomposition rate of acetylsalicylic acid. Eur J Pharm Biopharm. 1995;41: 114-119.

Hancock BC, Christensen K, Clas SD; Microscale Measurement of the Mechanical Properties of Compressed Pharmaceutical Powders, Part 1: The Elasticity and Fracture Behavior of Microcrystalline Cellulose. Int. J. Pharm., 2000; 209: 27–35.

Lachman L, Lieberman HA, Kanig JL; The Theory and Practice of Industrial Pharmacy. 3rd edition, Varghese Publishing House, Bombay. 1987: 294, 336, 413.

Lieberman HA, Lachman L, Schwartz JB; Pharmaceutical Dosage Forms, 2nd edition, Marcel Dekker Inc, New York.1989; 1: 195-229.

Mashadi AB, Newton JM; Assessment of the Mechanical Properties of Compacted Sorbitol. Instant. J. Pharm. Pharmacol., 1987; 39: 67.

Ohwoavworhua F, Adelakun T; Phospho- ric acid-mediated depolymerisation and decrystallization of a-Cellulose Obtained from Corn Cob: Preparation of Low Crystallinity Cellulose and Some Physicochemical Properties. Tropical journal of Pharmaceutical Research, 2004; 4(2): 509-516.

Shoukri RA, Ahmed IS, Shamma RN; In vitro and in vivo Evaluation of Nimesulide Lyophilized Orally Disintegrating Tablets. European Journal of Pharmaceutics and Biopharmaceutics, 2009; 73: 162–171.

Tejakrishna M, V.Sai Kishore, K.V.S. Prasada Rao, B.Sudheer, Formulation and Evaluation of Mucoadhesive Micro- beads of Glimepiride, Scholars Academic Journal of Pharmacy, 2013; 2(3):199-208.

Zinchuck AV, Hancock BC, Shalaev EY, Reddy RD, Govindarajan R, Novak E. The influence of measurement conditions on the Hammett acidity function of solid pharmaceutical excipients. Eur J Pha. 2005.