

pH Sensitive In-Situ Gelling Gastro-Retentive Drug Delivery System Of Esomeprazole For Management Of Peptic Ulcer Disease

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Abstract

Esomeprazole, a proton pump inhibitor recommended for the treatment of gastroesophageal reflux disease-related erosive esophagitis, is one of the frequently prescribed drugs for the treatment of peptic ulcer diseases. Owing to the poor oral bioavailability and half life of less than 2 hrs, the current work was aimed to formulate an in situ floating system for the delivery of Esomeprazole in a sustained manner using Xanthan Gum, Gelrite along with Calcium carbonate and citric acid with 3² factorial design. Xanthan gum, Gelrite and calcium carbonate were selected as independent variables. The prepared formulations were evaluated for viscosity, clarity, gelling strength, floating time, drug release and in-vivo gelation and floating study. All the batches have shown pH around 8 and good gelling capacity except E₁, E₂ and E₃. Viscosity and drug content of Raft formulation varied from 1343.33 to 7034.66 CP, 96.24 to 101.52 % respectively. The viscosity is positively influenced by concentration of Xanthan gum and Gelrite. Floating time differed from 5 seconds to 5 minutes where all formulations showed total floating time more than 12 hours except E₁, E₂ and E₃. In-situ gelation was observed at acidic pH with good gastric retention which was confirmed by gelation study conducted on Albino rats. X-Ray radiograph authenticated in-vivo gastric retention after administration of prepared in-situ gel. The release study indicates that present DDS delivers drug over a period of more than 12 hours. The factorial equation proved Xanthan Gum and Gelrite's concentration is dominant causing drug release retardation while concentration of Calcium carbonate is not having any effect on drug release.

Keywords: In-situ gel, Esomeprazole, Floating gel, Xanthan gum, Gelrite.

Key Points

Known Facts:

1. Frequent Administration of Esomeprazole for treatment
2. Available in tablet form
3. Floating System can be used to enhance bioavailability

Present Study adds:

1. Floating oral single dose in-situ gel of Esomeprazole
2. Effective in-vivo gelation and floating for more than 12 hrs.
3. Stable formulation during storage conditions.

Introduction

Due to fast gastric emptying time, oral formulations show low bioavailability. To overcome this, floating drug delivery systems are designed in a manner to have average bioavailability by releasing drug at desired rate for required period of time. Such systems are effective for drugs having absorption in stomach or small intestine (1-3).

Low-density systems called floating systems have enough buoyancy to float over the contents of the stomach without significantly slowing down the rate at which the stomach empties. The medicine is removed from the system slowly and at the desired pace while it is floating on the contents of the stomach (2-5).

Increased stomach retention duration and improved control of medication concentration changes are also outcomes of the floating system. A minimal degree of floating force (F) is also necessary to maintain the dose form consistently buoyant on the surface of the meal, and both are necessary for the appropriate attainment of the buoyancy retention principle. In order to create a stable sol/suspension system to hold the dispersed medication and other excipients, a gelling agent is used to create gastro retentive in situ gel systems. The gelling of this sol/suspension system is achieved in stomach environment, driven by ionic complexation due to change in pH (2, 3-5).

The unintentional transfer of stomach contents to the esophagus is known as gastroesophageal reflux. In most otherwise healthy people, gastroesophageal reflux occurs multiple times each day without causing any symptoms or harm to the esophagus mucosa. The illness known as gastroesophageal reflux disease causes the esophagus, pharynx, or respiratory tract to be damaged as well as frequent or severe symptoms that have a detrimental impact on a person's quality of life (3-7).

Esomeprazole selective and reversible proton pump inhibitor, forms a stable disulfide bond with the sulfhydryl group of the hydrogen-potassium ($H^+ - K^+$) ATPase found on the secretory surface of parietal cells, thereby inhibiting the final transport of hydrogen ions (through exchange with potassium ions) into the gastric lumen and suppressing gastric acid secretion (1, 3, 4). The present study was planned to formulate and evaluate the floating in-situ esomeprazole oral gel preparation.

Materials and Methods

Materials

Esomeprazole was received as gift sample from Zydus Cadila, Ahmadabad. All chemical and reagents used were of analytical grade.

Preparation of In situ Gelling Solution:

Xanthan gum and gelrite at different concentrations (0.25%, 0.5% and 0.75%) were added in distilled water containing Calcium carbonate (0.125%) and citric acid (0.125%). The drug solution was added to above solution with constant stirring. All ingredients weighed accurately and formulation were prepared as per Table 1. Water was used to dissolve esomeprazole. The solution containing the xanthan gum and the gellan gum was then supplemented with calcium carbonate and citric acid dissolved in water. The volume was brought to 60 ml with distilled water, and the medication solution was added to the mixture. The resulting solution was stored in amber colored bottles for further use (9).

Evaluation of prepared In Situ gel

Physical appearance and pH

All formulations were checked for their clarity, that is, color, homogeneity for presence of any physical particles. pH of all formulations was measured using a digital calibrated pH meter. The pH of each suspension was determined in triplicates (8-10).

Viscosity

The viscosity of formulations was determined by Brookfield Viscometer (DL/E). The samples were sheared at 10 rpm using spindle S63 at room temperature. Viscosity measurement was done in triplicate taking approximately 30 Sec (9).

In vitro Gelation Study

Gelation of in situ gelling solution was carried out by taking 500 ml of 0.1 N HCl in a beaker. Accurately measured 10 ml of solution was added to HCl with mild agitation that avoids breaking of formed gel. Gelling was observed visually by qualitative measurement (8).

In vitro Floating Study

Floating study of in situ gelling solution was carried out by taking 500 ml of 0.1 N HCl in a beaker. Accurately measured 10 ml of solution was added to HCl with mild agitation. Time required for floating on surface after adding solution (Floating lag time) and total floating time was measured (9, 11).

Determination of Drug Content

Weighing 0.5 ml of solution and performing repeated dilutions to measure absorbance in a UV-spectrophotometer at 280 nm allowed us to determine the esomeprazole concentration in the present formulation. A calibration curve was used to determine the actual amount of medication present. Using concentrations of 2, 4, 6, 8, and 10µg/ml as references, a calibration curve is constructed. Each sample's concentration was calculated by plotting its absorbance against a standard curve.

In vitro Drug Release Study

The in vitro release rate of Esomeprazole was performed using USP apparatus. Fitted with paddle (100 r/min) at 37± 0.5° C using 500 ml of 0.1 N HCl as a dissolution medium. This speed was slow enough to avoid the breaking of gelled formulation and was maintaining the mild agitation conditions believed to exist in vivo. At the predetermined time intervals, 10 ml samples were withdrawn, filtered through a 0.45 µm membrane filter, diluted and assayed using Systronic 2201UV double beam spectrophotometer. Cumulative percentage drug release was calculated using an equation obtained from a calibration curve (11-13).

In-Vivo Gelation Studies

The gelation studies were carried In vivo using rat as animal model. The animal was fasted overnight with free access to water. The gelling solution was then administered using oral feeding needle. The animal was sacrificed at the end of 30 min and visual inspection of the contents was carried out.

In vivo gastric retention study:

To confirm the gastric retention of the Gel, in vivo gastric retention studies were carried out. The method reported was modified to set up the protocol for carrying out the retention studies in the albino rat. (14) Adult male albino rat having body weight 180-220gm was selected. The animal was fasted overnight with free access to water to maintain adequate gastric fluid content. The animal was anaesthetized using Ketamine which was administered [0.5ml] by I.M. route. Dose of gelling solution corresponding to 100mg of Barium sulphate as X-ray contrast agent was then administered by oral route.

The retention was studied by monitoring the animal by taking X-Ray radiographs at regular intervals to check the retention of gelled mass containing barium sulphate. To confirm the gastric retention of the dosage form [Gel], in vivo gastric retention studies were carried out. The method reported by Sapphire S. et al [2010] and Miyazaki S. et al [2003] was modified to set up the protocol for carrying out the retention studies in the albino rat. Adult male albino rat having body weight 180-220gm was selected. The animal was fasted overnight with free access to water to maintain adequate gastric fluid content. The animal was anaesthetized using Ketamine which was administered [0.5ml] by I.M. route. Dose of gelling solution corresponding to 100mg of Barium sulphate as X-ray contrast agent was then administered by oral route. The retention was studied by monitoring the animal by taking X-Ray radiographs at regular intervals to check the retention of gelled mass containing barium sulphate.

Accelerated Stability Studies:

Stability testing of drug product being a part of drug discovery and ends with the commercial product, to assess the drug and formulation stability, stability studies were done. The stability study was carried out for the most satisfactory formulation. The most satisfactory formulation was sealed in a glass vial and kept at $40 \pm 2^\circ\text{C}$ and 75 ± 5 RH for 3 months. At the end of each month, the samples were analyzed for the parameters like Clarity, pH, and drug content.

Results and Discussions

Physical appearance and pH

All formulations were checked for presence of any physical particles or not. All the formulations were found to be clear. The average values of pH are given in Table 3.

Viscosity

The Viscosity of formulations varied from 1343.33 to 7034.66 (Table 1), indicating positive effect of Xanthan gum and Gelrite, the effect of concentration of Xanthan Gum and Gelrite is dominant than calcium carbonate.

The equation 1 and 2 shows the factorial analysis of Viscosity of floating in-situ gel containing Xanthan Gum, Gelrite and Calcium carbonate respectively.

$$Y = 5430.44 + 1490.445X_1 - 2737.110X_1X_2 \dots\dots\dots(1)$$

$$Y = 12.876 + 4.998X_1 - 5.299X_1X_2 \dots\dots\dots(2)$$

Table 7.3 shows the results of viscosity of all formulation. Viscosity of floating gel varied from 7034.66 to 1528.66 cps. Fig no. 1 and Equation 1 and 2 demonstrate the factorial analysis of the viscosity as dependent variable and concentration of xanthan gum, gellan gum and calcium carbonate are independent variables. It can be concluded from the equation 1 and 2 that viscosity is positively influenced by the concentration of polymers viz xanthan gum and guar gum. The concentration of calcium carbonate has not shown any significant effect on viscosity of formulation but

when the concentration of xanthan gum, gellan gum and calcium carbonate is increased, viscosity increases and further rise in concentration decreases the viscosity.

In vitro Gelation Study

Gelation was observed visually for all the formulations. The gelling strength are illustrated in Table 1. It can be observed that formulations with higher concentration of xanthan gum and guar gum show better gelling owing to the higher viscosity of the formulations as supported by the results of viscosity measurement. Higher concentration of xanthan gum and guar gum yields a gel with higher degree of cross linking which can be responsible for better gelation.

In vitro Floating Study

The Floating Lag Time and Floating Time were used to conduct a floating investigation of the in-situ gelling solution (Table 7.5). The lag time varied from 5 seconds to 5 minutes. The reason behind this may be higher concentration of Calcium carbonate releasing more CO₂ bubbles which helps in rapid floating whereas higher concentration of Xanthan gum and Gelrite making the gel heavier which takes time to float. The gelation of the formulation creating a hydrogel structure can also be attributed for good buoyancy.

Determination of Drug Content

The concentration of Esomeprazole gel in 0.1 N HCl was determined by using a UV visible spectrophotometer at a wavelength of 280 nm after several batches of the medicine were produced. Table 1 displays the results, which indicate that the assay is within acceptable parameters.

In vitro Drug Release Study

The in vitro release rate of esomeprazole was determined by dissolving 900 millilitres of the drug in 37± 0.5° C, 0.1 N HCl, at 100 revolutions per minute. Percentage cumulative drug release was determined using an algorithm derived from a calibration curve. Coefficient of correlation between the calibration curve and the data is 0.9993, indicating excellent linearity.

The dissolution study of all formulations shows that the drug release is retarded to approximate duration of 24 hours. (Fig.2) The release for all batches is given in Table 2The factorial equation as well as contour plot (Fig 3) shows that the concentration of xanthan gum is dominant and independent factor causing the retardation of drug release. This may be due to yield of gels with higher viscosity and crosslinking which causes resistance to the outflux of drug from the polymer matrices. The relationship was found to be concentration dependent for factor I i.e. Xanthan gum and Guar gum.

$$Y= 5430.4400 -9.5567X_1 \dots\dots\dots(3)$$

$$Y= 42.663 -4.205 X_1 \dots\dots\dots(4)$$

Drug dissolution profiles are shown in Fig 2 and 3. Sustained release of drug is a combined effect of Xanthan gum and Gelrite. The release was retarded up to 24 hours with higher of Xanthan gum and Gelrite concentration batches. T_{60%}(Time required for 60% dissolution) was found to be lengthened as the concentration of Xanthan gum and Gelrite increased. The n values are less than 0.5 for Batch E₂,E₆,E₇,E₈ and E₉, which indicates the Fickian Release while for other batches E₁,E₃,E₄ and E₅ the value of n is negative which reflects... The best fit dissolution models with most of the combinations were

Dissolution retardation is dependent on concentration of Xanthan Gum and Gelrite. It may be due to.....

In vivo Gelation Study

The gelation studies were carried in-vivo using rat as animal model. The animal was fasted overnight with free access to water. The gelling solution was then administered using oral feeding needle. The animal was sacrificed at the end of 30 min and visual inspection of the contents was carried out. There was formation of cohesive gel mass in the rat stomach. The gel had sufficient consistency and sufficient strength to be retained in stomach. Fig no. 4 and 5 reveals the gel mass as seen in the isolated rat stomach. Thus, it can be inferred that the sol gel transition In vivo, proceeds as it occurs in vitro, resulting in stable raft gel formation.

In vivo Gastric Retention Study

The prepared Esomeprazole floating in-situ gel containing xanthan gum and Gelrite along with calcium carbonate and citric acid were selected for evaluation of gastric retention using X-ray imaging. Figure 6 and 7 showed the gastric retention of gel in albino rats after 6 hours. The in vivo gelation was confirmed by X-ray imaging at 30 min regular time interval after ingestion of in-situ gel containing BaSO₄. The behaviour of the floating in-situ Esomeprazole gel in albino rat stomach was observed using a radiographic imaging technique. The in-situ gel seen in stomach of albino rats till 6 h (n = 3) showed the confirmation of buoyancy of the formulated gel.

Conclusion

The goal of the current effort was to create a brand-new gel-based in situ Esomeprazole medication delivery system. The technique used to make the in-situ gel solution was exceedingly straightforward and economical. It is a more recent method to enhance simple installation and residential longer medication release and bioavailability. By virtue of its capacity to prolong gastric residence time and sustain drug release, as well as its advantage of floating and pH that minimize the degradation of Esomeprazole the developed formulation is a viable substitute for conventional solution.

Table 1: Composition of Floating In Situ gel

| Ingredients | Formulation Code and Quantities | | | | | | | | |
|------------------------|---------------------------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
| | E ₁ | E ₂ | E ₃ | E ₄ | E ₅ | E ₆ | E ₇ | E ₈ | E ₉ |
| Esomeprazole (mg) | 240 | 240 | 240 | 240 | 240 | 240 | 240 | 240 | 240 |
| Xanthan gum (mg) | 150 | 150 | 150 | 300 | 300 | 300 | 450 | 450 | 450 |
| Gelrite (mg) | 150 | 150 | 150 | 300 | 300 | 300 | 450 | 450 | 450 |
| Calcium carbonate (mg) | 150 | 300 | 450 | 150 | 300 | 450 | 150 | 300 | 450 |
| Citric acid (mg) | 50 | 75 | 100 | 50 | 75 | 100 | 50 | 75 | 100 |
| Distilled water (ml) | 60 | 60 | 60 | 60 | 60 | 60 | 60 | 60 | 60 |

Table 2: Formulation of Floating In Situ gel

| Experimental Run | X ₁ | X ₂ |
|------------------|----------------|----------------|
| E ₁ | -1 | -1 |
| E ₂ | -1 | 0 |
| E ₃ | -1 | +1 |
| E ₄ | 0 | -1 |
| E ₅ | 0 | 0 |
| E ₆ | 0 | +1 |
| E ₇ | +1 | -1 |
| E ₈ | +1 | 0 |
| E ₉ | +1 | +1 |

| Coded Values | X ₁ Conc. of Xanthan Gum & Gelrite | X ₂ Conc. of Calcium Carbonate |
|--------------|--|--|
| -1 | 150 | 50 |
| 0 | 300 | 75 |
| +1 | 450 | 100 |

Table 3: Evaluation of Floating In Situ gel

| Formulation Code | pH | Gelling Capacity | Viscosity (CP) | Drug Content (%) | Floating Lag Time(Seconds) | Floating Time |
|------------------|---------|------------------|----------------|------------------|----------------------------|---------------|
| E1 | 8 ± 0.6 | + | 1528.66 | 97.5 | 5 | 20 min |
| E2 | 8 ± 0.5 | ++ | 2780 | 99.25 | 15 | 20 min |
| E3 | 8 ± 0.6 | + | 1343.33 | 99.5 | 95 | 20 min |

| | | | | | | |
|-----------|------------|------|---------|--------|-----|-----------|
| E4 | 8 ± 0.6 | ++ | 2734.66 | 97.5 | 300 | >12 Hours |
| E5 | 8 ± 0.5 | ++++ | 6476.66 | 101.52 | 70 | >12 Hours |
| E6 | 8 ± 0.6 | +++ | 2993.33 | 99.25 | 66 | >12 Hours |
| E7 | 8 ± 0.6 | +++ | 4100 | 99.75 | 82 | >12 Hours |
| E8 | 8 ± 0.5 | +++ | 7034.66 | 96.54 | 84 | >12 Hours |
| E9 | 8 ± 0.6 | +++ | 3460 | 97.29 | 98 | >12 Hours |

+ = Poor

++ = Good

+++ = Very good

++++ = Excellent

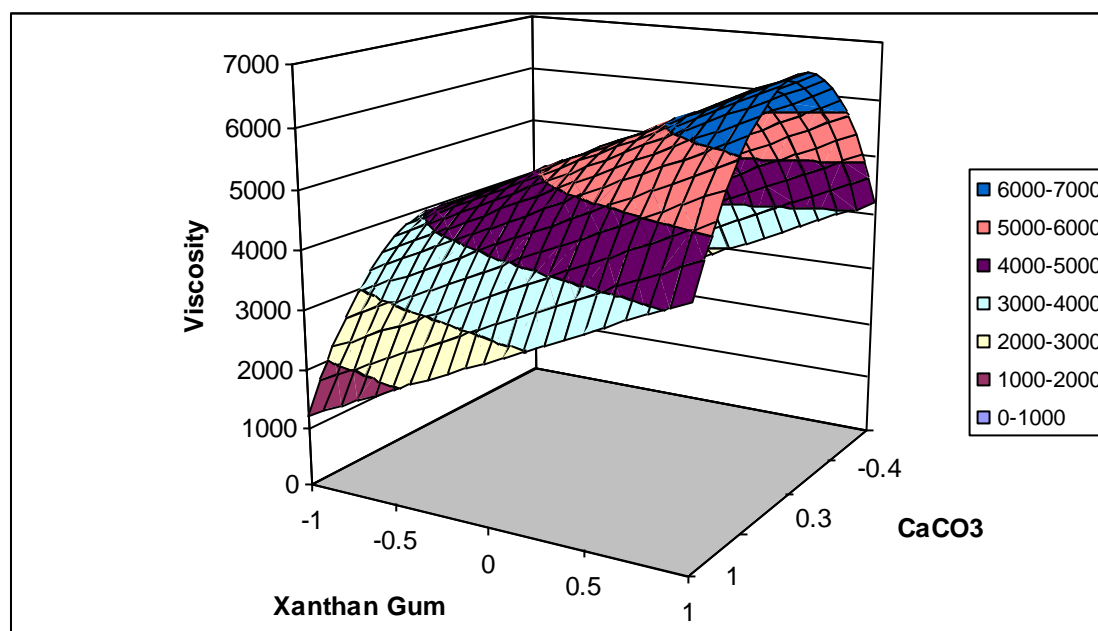


Fig 1 Contour plot for Viscosity

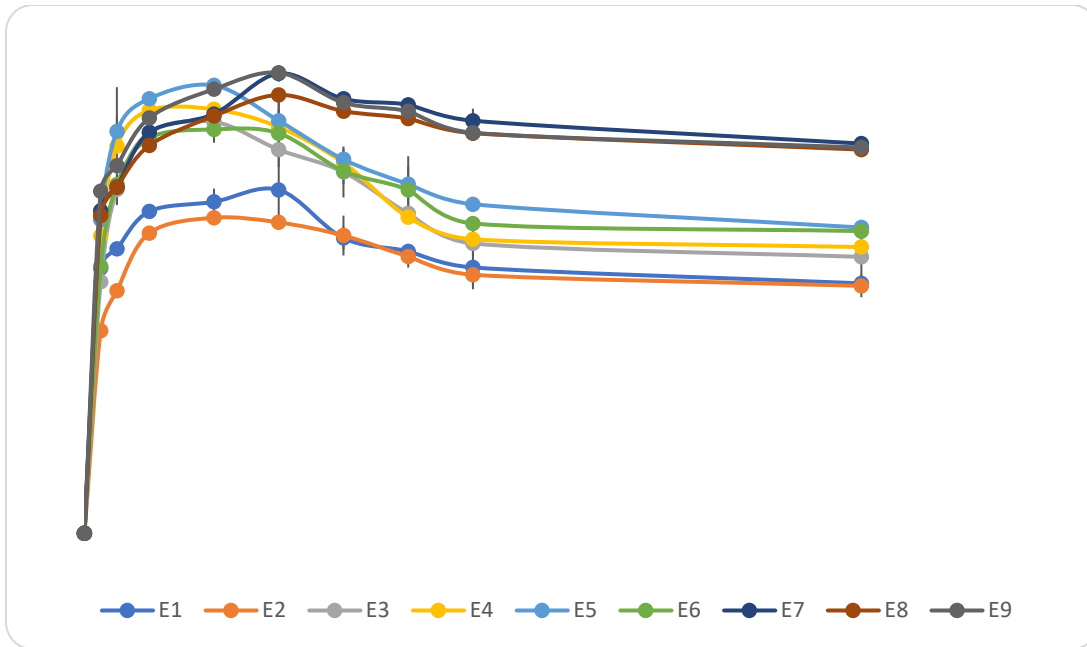


Fig 2 % Drug Release of Esomeprazole

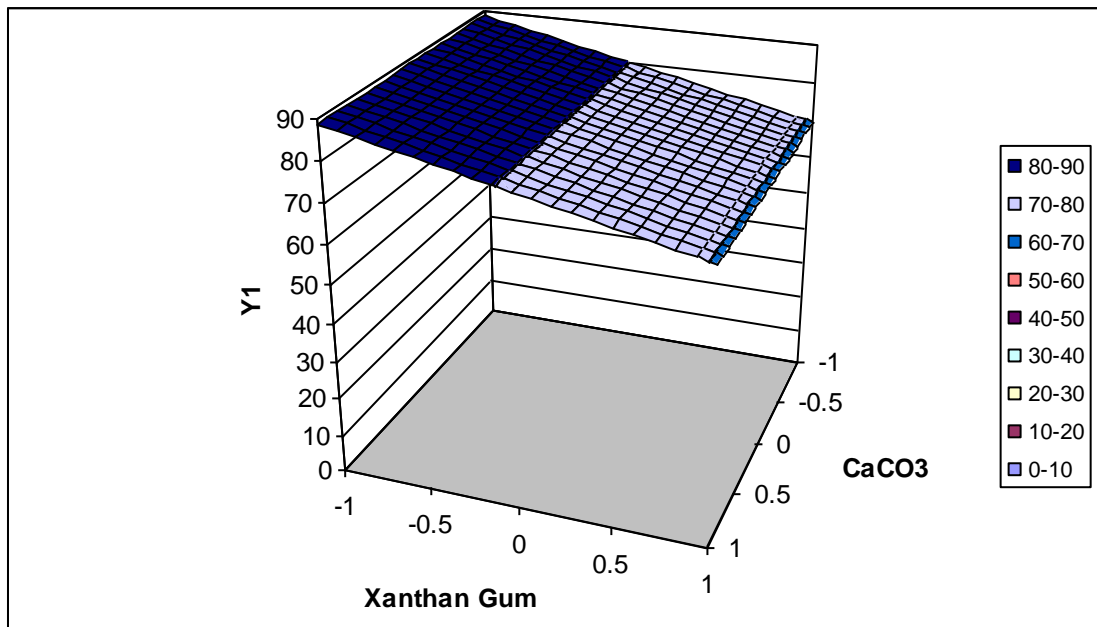


Fig 3 Contour plot for drug dissolution study of floating in-situ gel



Fig 4 In-vivo Gelation



Fig 5 Isolated rat stomach containing floating gel



Fig 6 X-ray radiograph (Immediate)

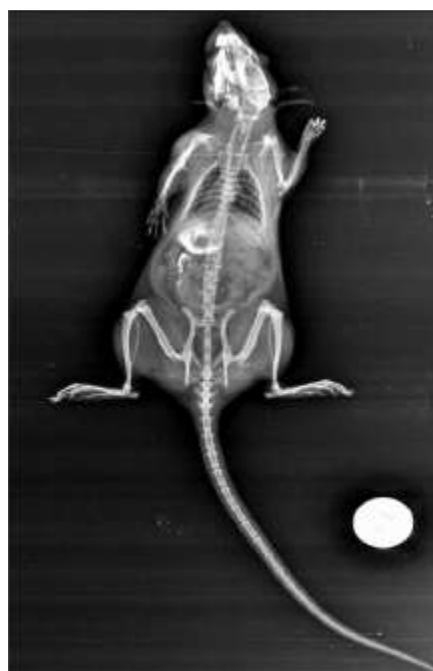


Fig 7 X-ray radiograph (After.6 Hrs)

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