Preparation and evaluation of matrix type gastro retentive floating atenolol tablets using sintering technique.

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ABSTRACT
The aim of this investigation was to design and assess the gastric floating tablets of Atenolol using thermal sintering and investigate the effect of sintering on PEO polymer. Atenolol is an Antihypertensive with only 50 percent bioavailability due to poor absorption in lower GI tract. Gastro retentive Floating tablets were prepared to enhance the gastric retention time, to prolong the drug release. PEO which was selected as sintered polymer. Tablets were prepared by direct compression method. Formulated tablets were exposed to different temperatures (40°C, 50°C and 60°C) at various time intervals (1h, 2h, 3h and 4h) in a hot air oven. Post compression parameters were evaluated like weight variation, hardness, friability, floating lag time and total floating time. The result of the investigation indicates sintering influenced the floating time and dissolution properties. Weight variation, friability and content uniformity values were within limits. Sintering time and temperature contributes to effectiveness of polymers in extending drug release. Reduction in floating lag time and increase in total floating time as well as release of drug was delayed. All sintered formulation have no interaction was found in FTIR, DSC studies. All sintered tablets followed zero order with non fickian diffusion mechanism. This study helps the use of thermal sintering in preparation of floating tablets.

INTRODUCTION
Sintering is defined as generation of welded bonds between polymer particles. Controlled release dosage forms were prepared by exposing the matrix tablet to temperature near melting point range of the polymer (Cohen et al., 1984). The temperature treatment involves the exposing the Tablet dosage form to particular temperature and the polymer forming the matrix slowly melts and the adhesive bondings are formed and leads to control the release of drug (Singh et al., 2007). The oral bioavailability of numerous medications are restricted due to negative physicochemical qualities or absorption in specific portion of the Body alluded as "Narrow absorption window" (Shahi et al., 2013). Prolonged gastric maintenance improves bioavailability; decreases medicate squander, and improve the dissolvability of drugs (Yadav and Jain, 2012). Gastroretentive Gastro retentive floating drug delivery helps to increment gastric living arrangement time in this way site explicit medication discharge in the upper gastrointestinal tract. Because of this prolonged gastric retention it helps to enhance drug absorption which leads better bioavailability with therapeutic efficacy (Baumgartner et al., 2000).

Atenolol was taken as a model drug. Mainly used in treatment of hypertension and angina. Atenolol
elimination half life is 6 to 7 hours and is incompletely absorbed from the lower GIT (Melander et al., 1979). Human jejuna permeability and absorption is low (Amidon et al., 1995). Hence, it appears that if increasing in gastro retentive floating time may improve the bioavailability of the drug. So the investigation was planned for developing floating drug delivery system with thermal sintering method. Selected polymer was PEO. In the present investigation this polymer is selected for sintering and proposed to study sintering effect on design of gastroretentive gastro retentive floating tablets.

MATERIALS AND METHODS

Materials
Atenolol was obtained from yarrowchem products (Ghatkopar, Mumbai). PEO obtained from the yarrowchem products (Ghatkopar, Mumbai). All other reagents and chemicals were of analytical grade.

Drug excipients compatibility study
Similarity contemplates were done understand the potential associations among drug and inactive ingredients. Physical blends of active ingredient and inactive ingredients in the proportion 1: 1 ratio were set up for examination the similarity. Drug polymer similarity ponders were done using FTIR spectroscopy. The IR spectra’s were recorded in the middle of 500–4000 cm$^{-1}$ (JR, 1965).

Methods

Calibration curve
Standard stock solution of atenolol done in methanol to a concentration of 100 mg/ml. Working Standard solutions were prepared from the stock standard solution by diluting with 0.1N Hydrochloric acid. Calibration graph was constructed in the range 5, 10, 15, 20, 25 μg/ml. The absorption peak maxima found at found at 225 nm (Figure 1).

Preparation of tablets
Table 1: Composition of floating tablets with gastroretentive effect

| Ingredients                | AP1  | AP2  | AP3  | AP4  | AP5  |
|----------------------------|------|------|------|------|------|
| Atenolol                   | 50   | 50   | 50   | 50   | 50   |
| PEO (WSR coagulant)        | 50   | 75   | 100  | 25   | 37.5 |
| Sodium bicarbonate         | 40   | 40   | 40   | 40   | 40   |
| Microcrystalline cellulose | 195  | 165  | 135  | 242.5| 230  |
| Magnesium stearate         | 2.5  | 2.5  | 2.5  | 2.5  | 2.5  |
| Talc                       | 350  | 350  | 350  | 350  | 350  |

Table 2: Tabletting and invitro buoyancy characteristics of unsintered tablets

| Formulation code | Weight in (mg) | Assay in (%) | Hardness in (kg/cm²) | Friability in (%) | Floating lag time in (sec) | Total floating time in (hr) |
|------------------|----------------|--------------|----------------------|-------------------|--------------------------|-----------------------------|
| AP1              | 348.9±1.09     | 98.8±1.98    | 4-6                  | 0.35              | 141                       | >12                         |
| AP2              | 350.8±1.87     | 101.3±1.23   | 4-6                  | 0.41              | 137                       | >15                         |
| AP3              | 350.5±1.43     | 100.1±1.56   | 4-6                  | 0.38              | 123                       | >17                         |
| AP4              | 353.1±1.63     | 99.8±1.75    | 4-6                  | 0.42              | 161                       | >6                          |
| AP5              | 348.9±1.73     | 100.2±1.02   | 4-6                  | 0.19              | 153                       | >8                          |

Table 3: Tabletting and invitro buoyancy characteristics of AP4

| Sintering temp and time | Weight in (mg) | Assay in (%) | Hardness in (kg/cm²) | Friability in (%) | Floating lag time in (sec) | Total floating time in (hr) |
|-------------------------|----------------|--------------|----------------------|-------------------|--------------------------|-----------------------------|
| unsintered              | 348.1±1.33     | 100.1±1.03   | 4-6                  | 0.32              | 161                       | >6                          |
| 40°C 1 hr               | 349±1.21       | 99.7±1.99    | 4-6                  | 0.45              | 158                       | >6                          |
| 40°C 2 hr               | 350.7±1.64     | 98.8±1.74    | 4-6                  | 0.31              | 154                       | >6                          |
| 40°C 3 hr               | 351.2±1.31     | 99.5±1.49    | 4-6                  | 0.19              | 150                       | >6                          |
| 40°C 4 hr               | 350±1.07       | 101.2±1.40   | 4-6                  | 0.32              | 144                       | >6                          |
| 50°C 1 hr               | 349.7±1.52     | 99.1±1.44    | 4-6                  | 0.43              | 146                       | >8                          |
| 50°C 2 hr               | 350.9±1.56     | 98.9±1.75    | 4-6                  | 0.41              | 134                       | >8                          |
| 50°C 3 hr               | 348.3±1.43     | 100.2±1.95   | 4-6                  | 0.24              | 129                       | >9                          |
| 50°C 4 hr               | 350.1±1.84     | 100.0±1.89   | 4-6                  | 0.37              | 117                       | >9                          |
| 60°C 1 hr               | 352.0±1.74     | 99.8±1.89    | 4-6                  | 0.45              | 119                       | >9                          |
| 60°C 2 hr               | 349.6±1.48     | 98.4±1.94    | 4-6                  | 0.23              | 102                       | >10                         |
| 60°C 3 hr               | 350.4±1.94     | 101.6±1.84   | 4-6                  | 0.34              | 96                        | >10                         |
| 60°C 4 hr               | 350±1.93       | 99.9±1.94    | 4-6                  | 0.42              | 84                        | >11                         |
Table 4: Tabletting and Invitro Floating characteristics of AP5

| Sintering temp and time | Weight in (mg) | Assay in (%) | Hardness in (kg/cm$^2$) | Friability in (%) | Floating lag time in (sec) | Total floating time in (hr) |
|-------------------------|----------------|--------------|-------------------------|------------------|--------------------------|---------------------------|
| unsintered              | 349.2±1.02     | 99.12±1.92   | 4-6                     | 0.21             | 153                      | >8                        |
| 40$^\circ$C 1 hr        | 350.1±1.11     | 100.3±1.62   | 4-6                     | 0.33             | 150                      | >8                        |
| 40$^\circ$C 2 hr        | 351.5±0.89     | 100.4±1.34   | 4-6                     | 0.41             | 148                      | >8                        |
| 40$^\circ$C 3 hr        | 352.5±1.45     | 99.1±1.09    | 4-6                     | 0.26             | 142                      | >8                        |
| 40$^\circ$C 4 hr        | 350.4±1.67     | 98.6±1.24    | 4-6                     | 0.32             | 134                      | >8                        |
| 50$^\circ$C 1 hr        | 348.7±1.32     | 100.6±1.04   | 4-6                     | 0.31             | 123                      | >10                       |
| 50$^\circ$C 2 hr        | 350.1±1.84     | 99.3±1.71    | 4-6                     | 0.12             | 114                      | >10                       |
| 50$^\circ$C 3 hr        | 351.6±1.31     | 100.5±1.02   | 4-6                     | 0.42             | 102                      | >11                       |
| 50$^\circ$C 4 hr        | 350.7±1.57     | 99.9±1.07    | 4-6                     | 0.27             | 83                       | >12                       |
| 60$^\circ$C 1 hr        | 350.9±1.82     | 100.3±1.10   | 4-6                     | 0.38             | 104                      | 10                        |
| 60$^\circ$C 2 hr        | 351.4±1.36     | 98.3±1.89    | 4-6                     | 0.31             | 89                       | >11                       |
| 60$^\circ$C 3 hr        | 349.5±1.42     | 100.7±1.32   | 4-6                     | 0.24             | 73                       | >12                       |
| 60$^\circ$C 4 hr        | 350.6±1.37     | 99.6±1.06    | 4-6                     | 0.32             | 66                       | >12                       |

Table 5: Coefficient of Correlation values and release of the kinetics of AP4

| Sintering temp and time | Zero order | First order | Higuchi model | Peppas model |
|-------------------------|------------|-------------|---------------|--------------|
| unsintered              | 0.9547     | 0.7328      | 0.8829        | 0.9715       |
| 40$^\circ$C 1 hr        | 0.9668     | 0.7994      | 0.9400        | 0.9929       |
| 40$^\circ$C 2 hr        | 0.9619     | 0.7433      | 0.9502        | 0.9929       |
| 40$^\circ$C 3 hr        | 0.9573     | 0.8563      | 0.9372        | 0.9762       |
| 40$^\circ$C 4 hr        | 0.9865     | 0.6932      | 0.8723        | 0.9637       |
| 50$^\circ$C 1 hr        | 0.9769     | 0.6783      | 0.8605        | 0.9700       |
| 50$^\circ$C 2 hr        | 0.9831     | 0.7694      | 0.8247        | 0.9413       |
| 50$^\circ$C 3 hr        | 0.9866     | 0.6737      | 0.8477        | 0.9571       |
| 50$^\circ$C 4 hr        | 0.9842     | 0.7840      | 0.8508        | 0.9665       |
| 60$^\circ$C 1 hr        | 0.9791     | 0.7376      | 0.8168        | 0.9495       |
| 60$^\circ$C 2 hr        | 0.9695     | 0.8711      | 0.7958        | 0.9481       |
| 60$^\circ$C 3 hr        | 0.9700     | 0.8417      | 0.7979        | 0.9498       |
| 60$^\circ$C 4 hr        | 0.9838     | 0.9232      | 0.8254        | 0.9589       |

Figure 6: DSC of Pure drug

Floating tablets of Atenolol were setup by direct compression method using PEO polymer. All excipients were weighed according to formulae (Table 1) and passed through sieve number 40 # and geometrically mixed for 5 min and then lubricated using...
Table 6: Coefficient of Correlation values and release of the kinetics of AP5

| Sintering temp and time | Zero order r | First order r | Higuchi model r | Peppas r | Peppas n |
|------------------------|-------------|--------------|----------------|---------|---------|
| unsintered             | 0.9773      | 0.7939       | 0.8976         | 0.9883  | 0.583   |
| 40°C 1 hr              | 0.9734      | 0.6756       | 0.8428         | 0.9652  | 0.552   |
| 40°C 2 hr              | 0.9804      | 0.6981       | 0.8436         | 0.9695  | 0.586   |
| 40°C 3 hr              | 0.9764      | 0.6666       | 0.8122         | 0.9476  | 0.565   |
| 40°C 4 hr              | 0.9621      | 0.7043       | 0.7570         | 0.9222  | 0.608   |
| 50°C 1 hr              | 0.9711      | 0.9260       | 0.8696         | 0.9662  | 0.525   |
| 50°C 2 hr              | 0.9647      | 0.9312       | 0.8136         | 0.9222  | 0.470   |
| 50°C 3 hr              | 0.9723      | 0.9636       | 0.8556         | 0.9682  | 0.524   |
| 50°C 4 hr              | 0.9651      | 0.9684       | 0.8626         | 0.9701  | 0.500   |
| 60°C 1 hr              | 0.9713      | 0.9075       | 0.7907         | 0.9279  | 0.529   |
| 60°C 2 hr              | 0.9762      | 0.9327       | 0.8384         | 0.9722  | 0.574   |
| 60°C 3 hr              | 0.9727      | 0.9779       | 0.8714         | 0.9766  | 0.530   |
| 60°C 4 hr              | 0.9865      | 0.9795       | 0.8484         | 0.9735  | 0.608   |

Magnesium stearate and talc for 3 min in a poly bag. Compressed tablets were exposed to 40°C, 50°C and 60°C for 4 different period of 1h, 2h, 3h and 4h in a hot air oven. After exposing to different temperatures remove the tablets and allowed to cool at room temperature.

Evaluation of tablets

Tablets had been evaluated for uniformity of weight, assay, hardness, in vitro buoyancy and dissolution studies.

Content uniformity of drug

Ten tablets were powdered and precisely weighed powder which is equivalent to 50 mg was transferred to a 100 ml of volumetric flask . flask to this add 0.1N HCl Solution and mixed carefully . Solution was made up to the volume 100 ml and filtered. 1ml was transferred and make up to 100 ml volume with 0.1 N HCl. Absorbance of the resulting solution was measured at 225nm using UV Visible Spectrophotometer. Estimation of Atenolol in tablet formulation was obtained from linearity equation of Calibration curve (Pawar et al., 2013).

In vitro buoyancy studies

Tablets were put into a 900 ml beaker containing 0.1N HCl . Floating lag time and total floating time was determined (Shekar et al., 2010).

In vitro dissolution studies

The drug release of all tablet batches were done in done in 900ml of 0.1 N HCl medium using USP Type II apparatus. RPM was maintained at 50 by maintaining the temperature at 37±0.5°C. The absorbance of the samples was conducted at different time intervals at 225 nm (Eswer, 2011).

Kinetics study

The drug release mechanism was assessed from floating tablets in the following models: Zero order: \( M = M_0 - K_0 t \); First order: \( \log C = \log C_0 - K t / 2.303 \); Higuchi model: \( Q = k t^{1/2} \); Korsemeyer: \( M_t / M_\infty = k t^n \) ; where \( M, C \), and \( Q \) are the drug release amount at time \( t \), \( M_0 \), and \( C_0 \) are gross drug release, and \( K_0, K \), and \( k \) are rate constant. Korsemeyer’s model: \( M_t / M_\infty \) is the fractional amount of drug release at time \( t \), \( k \) is a constant, \( n \) value is kinetic constant, which is denotes transport mechanism. The value of \( n \) for a cylinder is < 1.0 for Anomaloustransport (Nonickian diffusion), 1.0 indicates Case-II transport, >1.0 shows Super Case-II transport (Singh et al., 2011).

Differential scanning calorimetry

Samples were measured and hermetically sealed in flat bottomed aluminium pans. These samples were heated over a range of 30 – 250°C at a constant constant rate of 5°C per minute in nitrogen atmosphere and recorded at a constant speed of 10mm per minute (Botha and Lötter, 1990).

RESULTS AND DISCUSSION

Both “Un sintered and warm sintered tablets” were tested for hardness in kg/cm², % weight variation, % friability, % drug content, in vitro buoyancy and in vitro dissolution studies. Tablets hardness were in the range 4-6 kg/cm². Estimated drug content was within 98.3% - 101.6 %. Friability test was found to be less than 0.5%. The percentage variation of weight was within the limits of ±5%. (Tables 2, 3 and 4). In vitro floating test of un sintered and sintered tablets were within the range of 66 to 161 sec.
It was observed that floating lag time was reduced due to concentration of polymer. After sintering floating time was decreased with the increase in sintering temperature may be due to decreasing porosity. Un sintered and sintered tablets Total time of floating were within range of 6-17 h. Total Floating time was increased with the increase in sintering temperature may be because of strong bonding between the particles formed. So if sintering time was increased it improves In vitro buoyancy. Dissolution profile of AP1, AP2 and AP3 un sintered tablets retarded the drug release upto 12, 15 and 17 h respectively. From the dissolution data it was noted that dissolution profile was not altered for formulation of AP 4 and AP5 when it was exposed to 40°C. The formulation AP4 tablets kept at 50°C for 1, 2, 3 and 4h and the drug release is more than 97%. AP4 tablets exposed to 60°C for 1, 2, 3, and 4h drug released more than 97%. Formulation AP5 with outwithout sintering condition the drug released upto 8h and the tablets of AP5 formulation at 50°C for 1h, 2h, 3h, and 4h retarded the drug uptov to 10h, 10h, 11h and 12h respectively and at 60°C for 1h, 2h, 3h, and 4h prolonged the drug release uptov to 10h, 11h, 12h, and 13h. It is evident from the data that if temperature and time of exposure increases the retarding power of polymer was increased. Dissolution profile of the formulation are given in Figures 2 and 3.

Results of kinetic models for AP4 and AP5 are given in Tables 5 and 6. In case of AP4 follows the zero order with Non-fickian diffusion. Whereas sintered formulation of AP5 follows zero order with non-fickian anomalous diffusion. Sintered formulation AP5 at 50°C for 1h, 2h, 3h, and 3h follows zero order with non-fickian anomalous diffusion. At 60°C exposed for 1h, 2h, 3h, 4h follows zero order with non-fickian anomalous diffusion.

The formulation AP5 sintered at temperature 50°C for 4h was selected as an optimized because low polymer concentration compared to AP1 to AP3 and after sintering at low polymer concentration drug release was retarded upto 12h.

**FTIR Studies**

The results of spectral analysis showed the major peaks for atenolol shows C-H stretch at 2959 cm⁻¹, C=N stretch at 1633 cm⁻¹, N-H bend at 1514 cm⁻¹, C-O stretch at 1237 cm⁻¹. Since there have been no major changes in the absorption peaks drug polymer interactions were ruled out. Spectrum were shown in Figures 4 and 5.

**DSC**

DSC of pure atenolol showed endothermic melting peak at 155.56°C. Based on thermogram there is no polymeric change in the drug due to sintering Figures 6 and 7.

**CONCLUSIONS**

With less polymer concentration desired dissolution was obtained by applying thermal sintering. Not only that it can canc the floating character was improved with temperature exposure length. Drug release retarding was maintained well when exposed to sintering temperature. Hence sintering method can be used for the formulation of gastric floating tablets of atenolol with PEO.

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