International Journal of Pharmaceutical Development & Technology

www.ijpdt.com

e ISSN - 2248 - 910X

Print ISSN - 2248 - 9096

# *IN VITRO* EVALUATION OF GASTRO RETENTIVE FLOATING DRUG DELIVERY SYSTEM FOR PINDOLOL BILAYER TABLETS

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**ABSTRACT**

Floating microspheres of Pindalol was prepared by ionic gelation method with an aim of increasing the gastric residence time and for controlled release. Sodium alginate, polymeric mixture of Sodium alginate and xanthan gum were used as polymers. Sodium bicarbonate was used as the gas-forming gent. The prepared floating microspheres were evaluated with respect to particle size distribution, floating behaviour, drug content, entrapment efficiency, morphology and in vitro release study. These results indicated that the release rate was found to decrease with increase in concentration of coating material applied. The wall thickness of microspheres was found to be increased with the increase in concentration of coating material applied. The floating microspheres followed zero order kinetics and the mechanism of drug release was governed by peppas model. For all the microspheres the exponential coefficient values were found to be in between 0.997 and 0.99988, indicating non fickian diffusion controlled release mechanism.

**Keywords:** *In vitro* evaluation Pindolol, Pre formulation evaluation.

## INTRODUCTION

Oral route is the most preferred route for administration of drugs. Among all tablets are the most popular oral formulations available and preferred by the patients and physicians alike.1 In long-term therapy for the treatment of chronic disease conditions, conventional formulations are required to be administered in multiple doses, and therefore have several disadvantages. Hence, Controlled release (CR) tablet formulations are much desirable and preferred for such therapy because they offer better patient compliance, maintain uniform drug levels, reduce dose and side effects, and increase safety margin for high potency drugs.[2-3]

## DRUG PROFILE

Pindolol is a synthetic beta-adrenergic receptor blocking agent with intrinsic sympathomimetic activity is 1-(Indol-4-yloxy)-3-(isopropylamino)-2-propanol. Pindolol is a white to off-white odorless powder soluble in organic solvents and aqueous acids. Visken (pindolol) is intended for oral administration

## METHODOLOGY

### Analytical method development

### Determination of absorption maxima

The drug Pindlolol was brought from Zydus Cadila Pharmaceuticals, polymer brought from Cipla Laboratories and analytical grade chemicals were used for the study.

### Preformulation Studies

Colour and Appearance, Melting Point, pH Determination, Solubility, UV Spectral Analysis (Water, 0.1Hcl, Phosphate buffer pH 7.4, Phosphate buffer pH 6.8 containing rat caecal contents) Infrared Spectrum and Loss on drying. Drug - Polymers Compatability Studies (FTIR and DSC). Evaluation of Micromeritic Properties of Granules (Angle of Repose, Bulk Density and Tapped Bulk Density, Carr's Compressibility Index and Hausner's ratio).

### Formulatin and Evaluation Methods

Formulation of Tablets (Wet granulation method). Evaluation of Tablets Properties of Tablets – Appearance, Size and Thickness, Hardness, Friability, Weight variation, Content uniformity, Swelling Index of Tablets, *In-vitro* Drug Release Studies , Kinetics of *In-vitro* Drug Release (Zero order, First order, Higuchi and Korsmeyer Peppas) and Stability Studies.

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The colon targeted matrix tablets containing GG, XG, EC and CAP were prepared by wet granulation method. Lactose was used as a diluents and mixture of Talc and Magnesium stearate (1:1) was used as a glidant and lubricant respectively. The composition of matrix formulation was shown in Table. Accurate quantity of drug and all ingredients were weighed according to formula shown in Table and mixed well except Magnesium stearate and Talc. Passed all the ingredients through mesh No. 250 separately except Magnesium stearate and Talc. Granulated the powder blend with granulating solution, prepared above and mixed for 15 minutes. Passed wet mass through mesh No. 12 to prepare wet granules. These wet granules then dried at $50^0$C for 30 min, passed the dried granules through mesh No. 22 superimposed on mesh No. 44. Finally Magnesium stearate and Talc were added. Accurately weighed 550 mg granules were fed manually in to 16 stations Cadmach tablet compression machine and compressed with 14 mm flat faced punches.

The Angle of repose ranged from 22.33 ± 0.64 to 23.48 ± 0.24. The flow properties of granules in all formulations exhibit good flow. The values of BD and TBD were found to be in the range from 0.541 ±0.005 to 0.553 ± 0.005 gm/ml and from 0.62 ± 0.007 to 0.64 ± 0.01 gm/ml respectively. So, it shows that all formulations having good flow properties and packability. The Carr's Compressibility Index were in the ranged from 12.160 ± 0.019 to 14.34 ± 1.236 %. This indicates good flow properties of granules. The Hausner's ratio were found in the ranged from 1.133 ± 0.023 to 1.160 ± 0.019. So it indicates good flow properties.

The tablets were observed visually and did not show any defects such as capping, chipping and lamination after punching. The thickness of formulations ranged from 4.11 ± 0.01 to 4.17 ± 0.010 mm. The percentage deviation from average tablet weight for all the formulations ranged from 0.99 to 1.54 %. The results are within the specified limits and showed in Table 28. Hence all formulations complied with the test for weight variation as per IP. The results of Hardness of tablets were recorded in Table 28. It was found that the values are ranged from 6.16 ± 0.258 to 7.25 ± 0.273 kg/cm$^2$. Hardness values were satisfactory and indicated good mechanical strength of tablets. The Percentage Friability of all the formulations showed in Table 28. The results are ranged from 0.27±0.030 to 0.42±0.023%. So, the percentage loss of Friability of all the formulations was found to be less than 1 %. Drug content was found to be uniform among different batches of tablets and ranged from 96.37 ± 1.831 to 103.27 ± 1.521%. These results showed that the all formulations having percentage drug content within the specified limits as per USP.Formulation CT2 showed the highest swelling index. This may be due to the increased viscosity of the XG in presence of GG than the GG alone and GG in combination with EC and CAP.

It can be observed that the swelling Index of different formulations decreased in the following order; CT2 > CT1 > CT4 > CT3 > CT7 > CT5 > CT8 > CT6.

The ability of the gums used in the formulations (CT1 to CT8) to retain the integrity of tablets in upper GIT were assessed by conducting drug release studies in 0.1N HCl for 2 hours and pH 7.4 phosphate buffer for 3 hours (condition mimicking mouth to the colon transit). After 5 hours of testing not more than 6% of Pindlolol was released from any formulations (CT1 to CT8). This shows that GG, XG, EC, CAP are capable of protecting the drug from being released completely in the physiological environment of Stomach and Small Intestine. On exposure to dissolution fluids, a gum undergoes hydration and forms the viscous gel layer that slows down further seeping-in drug dissolution fluid towards the matrix tablet. The initial drug release may be contributed to the dissolution of the drug from the surface of the matrix tablets and lag time required for the complete hydration of gums to form viscous gel layer around the tablet. After completing the dissolution study in 0.1 N HCl (900ml) for first two hours and in phosphate buffer pH 7.4 (900ml) for next three hours, the dissolution study was continued in the phosphate buffer pH 6.8 containing rat caecal contents (100ml) up to the twelve hours. The drug release from formulation CT1 containing GG alone was found to be 72.203% after the end of 12 hrs. This is due to lesser buffer uptake capacity of guar gum alone. But the Formulation CT2 containing GG + XG showed the drug release of 76.10% at the end of 12 hours. This maximum drug release may be due to the highest Swelling Index of this formulation. Results of drug released from formulation CT3 and CT4 containing EC and CAP in combination with GG were found to be 50.19% and 61.88% respectively at the end of 12 hrs. The drug released from formulation CT5-CT7 containing different combinations of XG, EC and CAP along with GG were found to be 54.64%, 54.06% and 43.72% respectively at the end of 12 hrs. CT8

**Table 1. Composition of Colon Targeted Matrix Tablets of Pindlolol**

| Sl. No. | Ingredients (mg/tablet) | Formulations Code | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | MF1 | MF2 | MF3 | MF4 | MF5 | MF6 | MF7 | MF8 |
| 1 | Pindalol | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 |
| 2 | Guar gum | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 |
| 3 | Xanthan gum | --- | 120 | --- | --- | 60 | 60 | --- | 40 |
| 4 | Ethyl cellulose | --- | --- | 120 | --- | 60 | --- | 60 | 40 |
| 5 | Cellulose acetate phthalate | --- | --- | --- | 120 | --- | 60 | 60 | 40 |
| 6 | Starch paste (8%) | q. s. | q. s. | q. s. | q. s. | q. s. | q. s. | q. s. | q. s. |
| 7 | Magnesium stearate | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| 8 | Talc | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| 9 | Lactose | 140 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |

**Table 2. Evaluation of Micromeritic Properties of Granules**

| Formulations Code | Angle of Repose (θ) (°) | BD (gm/ml) | TBD (gm/ml) | Carr's Index (%) | Hausner's ratio |
|---|---|---|---|---|---|
| CT1 | 23.13±0.62 | 0.544±0.006 | 0.62±0.007 | 13.62±0.161 | 1.150±0.006 |
| CT2 | 22.33±0.64 | 0.542±0.009 | 0.64±0.004 | 14.34±1.236 | 1.160±0.019 |
| CT3 | 22.39±0.12 | 0.541±0.005 | 0.63±0.007 | 13.37±0.206 | 1.152±0.004 |
| CT4 | 22.43±0.11 | 0.547±0.002 | 0.64±0.004 | 13.58±0.181 | 1.153±0.006 |
| CT5 | 22.43±0.99 | 0.553±0.005 | 0.63±0.01 | 12.06±1.512 | 1.133±0.023 |
| CT6 | 22.76±0.12 | 0.553±0.011 | 0.64±0.01 | 14.12±1.870 | 1.153±0.055 |
| CT7 | 23.48±0.24 | 0.552±0.007 | 0.63±0.003 | 12.76±0.435 | 1.143±0.021 |
| CT8 | 22.78±0.20 | 0.550±0.009 | 0.63±0.006 | 12.83±1.539 | 1.143±0.021 |

**Table 3. Evaluation of Tablets**

| Formulations Code | Thickness** (mm) | Weight Variation (%) | Hardness** (kg/cm$^2$) | Friability* (%) | Drug Content* *(%)* |
|---|---|---|---|---|---|
| CT1 | 4.11±0.01 | 1.48 | 6.33±0.258 | 0.29±0.096 | 97.49±1.134 |
| CT2 | 4.13±0.01 | 1.54 | 6.25±0.273 | 0.27±0.030 | 103.27±1.521 |
| CT3 | 4.13±0.016 | 1.14 | 6.75±0.273 | 0.33±0.074 | 99.41±0.760 |
| CT4 | 4.17±0.010 | 1.38 | 6.83±0.258 | 0.34±0.025 | 96.37±1.831 |
| CT5 | 4.15±0.019 | 1.38 | 7.25±0.273 | 0.42±0.023 | 96.39±1.069 |
| CT6 | 4.14±0.015 | 1.23 | 6.16±0.258 | 0.34±0.008 | 97.39±0.712 |
| CT7 | 4.15±0.010 | 1.30 | 6.75±0.265 | 0.38±0.052 | 103.06±0.609 |
| CT8 | 4.16±0.012 | 0.99 | 6.33±0.258 | 0.35±0.008 | 100.98±0.977 |

**Fig. 1. Swelling Index**

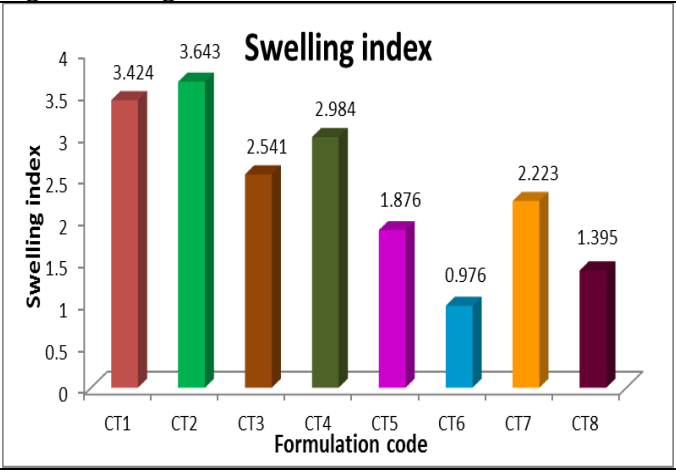
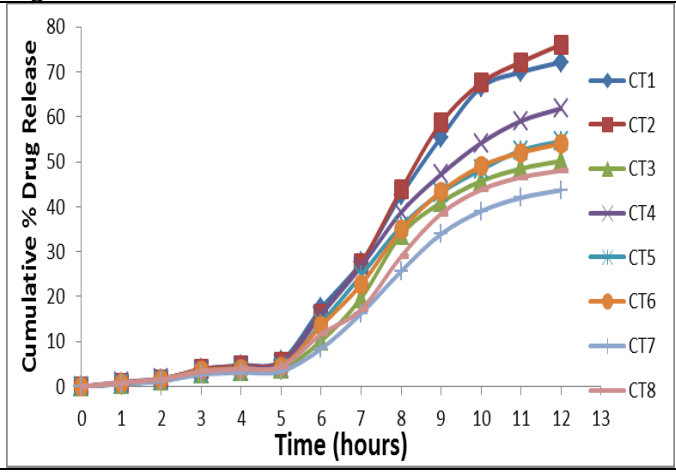



**Fig. 2. *In Vitro* Dissolution Studies**



formulation containing all the polymers shows the drug release of 48.05%. Drug release from all the tablet formulations followed diffusion control mechanism with $R^2$ value nearer to one.

For matrix tablets, an "n" value near to 0.5 indicates diffusion control and an "n" value near to 1 indicates relaxation or erosion control. The intermediate value suggests that diffusion and erosion contributes to overall release mechanism. A value of "n" for all matrices studied here was ranged between 2.2899 and 2.9792 indicating an anomalous behavior corresponding to swelling, diffusion and erosion mechanism. It was also observed that highest correlation was found for Peppas log time profile ($R^2 > 0.99$), which indicates the drug release via diffusion mechanism from all matrix formulations.

**Stability Studies**

No statistically significant differences were observed in Hardness, percentage drug content and cumulative percentage drug release in optimized formulation at the end of three months of stability studies. So it can be concluded that the formulation is stable for short term storage conditions.

**CONCLUSION**

The optimized formulation CT2 was subjected for stability studies, the formulation was found to be stable in short term stability study. From the *in-vitro* dissolution data, it can be concluded that the GG, XG, EC and CAP are capable of protecting the drug from being released in Stomach and in Small Intestine. This retardant capacity is more in CT2 as compared to CT1. During the *in-vitro* dissolution study, on exposure to the dissolution fluid, the matrix material becomes hydrated and forms a viscous gel layer that slows down further seeping-in of dissolution fluids towards the interior of the tablet. Once the gel layer is formed the drug release takes place mainly by diffusion from the inner region. Mechanical erosion also plays a role in drug release in case of matrix tablets. On reaching the colonic environment the swollen polymeric layer would be acted upon by the colonic bacterial enzymes and release the major amount of drug contained in the matrix tablet. In the *in-vitro* dissolution study, the drug release from the matrix tablet required a longer time in experimental conditions. This was because of limited caecal content in the dissolution medium (4% w/v). But in actual use in living systems these limitations for micro-organisms and its enzymes will never be felt. Therefore the matrix tablets disintegration will take place completely and rapidly. Formulation CT2 showed the highest swelling index. This may be due to the increased viscosity of the XG in presence of GG than the GG alone and GG in combination with EC and CAP. While analyzing the dissolution pattern of the drug from the matrix tablet, it was found that the drug release started in the early hours of study. This was due to the surface erosion of the matrix material. Out of the eight formulations, it appears that CT2 has the maximum potential in providing colon targeted drug delivery.

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