FORMULATION & EVALUATION OF BILAYER FLOATING TABLETS OF
METOPROLOL TARTRATE

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Abstract
The objective of the present research was to develop a bi-layer tablet of Metoprolol tartrate using disintegrant starch for the fast release layer and HPMC K grade polymers for the sustaining layer. In vitro dissolution studies were carried out in an Indian Pharmacopoeia dissolution testing apparatus II (paddle method). The formulations gave an initial burst effect to provide the loading dose of the drug followed by sustained release for 12 h from the sustaining layer of matrix embedded tablets. The In-vitro release study of this tablet indicated sustained release for Metoprolol tartrate and followed zero order release and 95% drug in 24h in vitro and it follow Fickian diffusion.

Keywords: Gastroretention; Oral controlled release; floating drug delivery system; hydrodynamically balanced system

1. Introduction
Oral administration is the most versatile, convenient and commonly employed route of drug delivery for systemic action. Indeed, for controlled release system, oral route of administration has received the more attention and success because gastro intestinal physiology offers more flexibility in dosage form design than other routes. Development of a successful oral controlled release drug delivery dosage form requires an understanding of three aspects: (1) gastro intestinal (GI) physiology (2) physiochemical properties of the drug and (3) dosage form characteristics.

The floating systems include gas-generating systems, noneffervescent systems and raft forming systems. Under certain circumstances prolonging the gastric retention of a delivery system is desirable for achieving greater therapeutic benefit of the drug substance. For example, drugs that are absorbed in the proximal part of the gastrointestinal tract and drugs that are less soluble in or are degraded by the alkaline pH may benefit from prolonged gastric retention. In addition, for local and sustained drug delivery to the stomach and proximal small intestine to treat certain conditions, prolonged gastric retention of the therapeutic moiety may offer numerous advantages including improved bioavailability and therapeutic efficacy, and possible reduction of dose size. It has been suggested that prolonged local availability of antibacterial agents may augment their effectiveness in treating Helicobacter Pylori related peptic ulcers. The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion, flotation, sedimentation, expansion, modified shape systems, or by the simultaneous administration of pharmacological agents that delay gastric emptying. When the drug is formulated with a gel forming polymer such as semisynthetic derivatives of cellulose, it swells in the gastric fluid with a bulk density less than one.

Metoprolol tartrate is a beta-1 adrenergic blocker, has been widely used in the treatment of Hypertension, angina pectoris, pheochromocytoma and cardiac arrhythmias (1). Because of its relative short plasma half, patients are routinely asked to take Metoprolol tartrate in divided daily doses, once every 6 to 8h. Such frequent drug administration may reduce patient compliance and therapeutic efficacy. In recent years, slow or sustains release formulation of Metoprolol tartrate have become available with claim that these formulation maintain beta adrenoreceptor blocked
throughout 24h period enable the drug to be given once daily (3). The multilayer tablet concept has been long utilized to develop sustained release formulations such a tablet has a fast releasing layer and may contain bi or tri layers to sustain the drug release (4). The pharmacokinetic advantage relies on the fact that drug release from fast releasing granules leads to a sudden rise in the blood concentration. However blood level is maintain at steady state as the drug is released from the sustained granules. Among the different polymers, the HPMC K grades have been successfully used to obtain appropriate sustained release matrix formulation of different materials. The present study aims at formulating bilayer tablets of Metoprolol tartrate with fast release layer using soluble starch and a sustaining layer using HPMC K grades polymers. The following tests were performed for all the batches.

### 2. Materials and Methods

#### 2.1 Materials:
Metoprolol tartrate was obtained from Astra Zeneca pharmaceuticals limited, (Bangalore India). Methocel k4000 and k15000cp, sodium carboxymethylcellulose and polyvinylpyrrolidone (PVP k30), soluble starch, magnesium stearate, talc and Lactose were supplied by (CDH (P) Ltd, New Delhi).

#### 2.2 Preparation of Immediate release dose:
First, drug-loading granules (as an immediate dose) were prepared by mixing MT, starch, PVP, and Lactose, using water as a wetting agent. The granules were dried at 60°C for 30 minutes in an oven and then mixed with talc, sunset yellow, and magnesium stearate (the composition is shown in table 1).

#### 2.3 Preparation of Sustained dose:
Floating granules containing Metoprolol tartrate were prepared by mixing the drug with excipient in a formulation as shown in Table-1. The granules were then dried at 60° for 30 minutes in an oven and then mixed with talc, and magnesium stearate (the composition is shown in table 2). Exactly 300mg of Floating granules and 100mg of drug loading granules were weighed and compressed into bilayer tablet by a single punch tablet compression machine (Jyoti scientific industries, Gwalior.).

#### 3. Characterization of powder

### 3.1 Bulk density
Bulk density=M/Va
Where, M =Mass of the powder taken, Va= Apparent volume

### 3.2 Tapped density
Tapped density=M/Vf
Where, M= weight of sample powder taken, Vf= Final tapped volume

### 3.3 COMPRESSIBILITY INDEX
C.I= {(Df-Do)/Df} *100
Where, Do= Bulk density
Df= Tapped density

### 3.4 HAUSNER RATIO
Hausner ratio=Df/Do
Where, Do=Bulk density, Df Tapped density

### 3.5 ANGLE OF REPOSE
\[
\tan \theta = \frac{h}{r}
\]
Or \[
\theta = \tan^{-1} \frac{h}{r}
\]
Where, \( h \) = height of pile, \( R \) =radius of the base of the pile and \( \theta \) = angle of repose

### 4. Evaluation of metoprolol tartrate bilayer tablet

#### 4.1 Hardness:
The tablet was placed between two anvils of hardness tester (Monsanto) and increasing amount of force (kg) was applied. The reading at the marked scale was recorded for the pressure which is required to break the tablet. Result was shown in Table 3.

#### 4.2 Friability:
Twenty tablets were weighed and placed in the Roche friability and apparatus was rotated at 25 rpm for 5 minutes after revolutions the tablets were dedusted and weighed again. The observed value should not be more than 1%. The percentage friability was measured using the formula.

\[
\% F = \left(1 - \frac{W_t}{W}\right) \times 100
\]
Where, \( \% F \) =Friability in percentage, \( W \)=Initial weight of tablet, \( W_t \)=weight of tablets after revolution. Result was shown in table 3.

#### 4.3 Drug content:
Five tablets for each batch was taken and triturated. Powder equivalent to 100mg of drug was weighed and was transferred to breaker and 0.1N HCL was added and it was then shaken for 5 minutes and finally 0.1N HCL was added to make the volume up to 100ml and solution was then sonicated for 15 minutes and filtered through Whatman filter paper. Finally a solution was
diluted suitably and the absorbance of resultant solution was measured spectrophotometrically at 275nm using UV/Visible spectrophotometer jasco V-530 against 0.1N HCL blank. Result was shown in table 3.

4.4 In Vitro release study: The release rate of Metoprolol tartrate floating tablets was determine using reported method in Indian Pharmacopoeia dissolution testing apparatus II (paddle method). The dissolution test was carried out under sink condition. At appropriate time interval (0.25,0.5,1,2,3,4,5,6,8,12 hrs) 5ml samples were withdrawn from dissolution media and was replaced with fresh media to maintain the volume constant. After dilution and filtration, the sample solution was analyzed by UV spectrophotometer at 275 nm. The amount of drug present in the sample was calculated by Cumulative percentage of drug release method. Cummulative percentage release of various batches was shown in table 4.

4.6 Floating time and floating lag time: Floating time indicates the time for which the tablet remains floating on the surface of the dissolution medium and floating lag time is the time required to reach the surface of the dissolution medium. Floating lag time of various batches was shown in table 4.

5. Data treatment11, 12, 13: In vitro dissolution has been recognized as an important element in drug development. Several kinetics models describe drug dissolution from immediate and modified release dosage form. In case of Korsemeyer’s model, n is a kinetic constant, which is used to characterize the transport mechanism. The exponent n determines release mechanism as given in table no 5. From the above equations the correlation coefficient and exponential (n) values for different formulations have been calculated to identify the drug release mechanism and are shown in table no 6-9.

6. Result & Discussion
The different models of data treatment are shown in above. To find out the mechanism of drug released from all the formulations of Metoprolol tartrate Bilayer floating tablets, the data were treated according to zero order, first order, Higuchi square root law and Korsemeyer’s equation pattern. As clearly indicated in Table no. 6, the correlation coefficient value of all the formulations showed that the formulations did not follow zero order release pattern but batch F1, F2 and F6 showed fair zero order. When the data were plotted according to the first order equation, the formulations showed a fair linearity, with correlation coefficient values between 0.812 to 0.983 (Table no. 6).

As gradient varies, the drug is released and the distance for diffusion increased. This explains the drug diffuses at a comparatively slower rate as the distance for diffusion increases, which is referred as square root kinetics or Higuchi’s kinetics (Table no.6). In this experiment, the in vitro release profiles of drug from all the plots showed high linearity (r² = 0.936 to 0.977). This represents the release process under the drug diffusion through polymer matrix. To confirm the diffusion mechanism, the data were fitted to Korsemeyer’s equation, F6; F7 (Table No. 6) formulation showed linearity with exponent value (n) ranging 0.34, 0.31. This n value however, indicates the coupling of swelling and diffusion mechanism so called as Fickian diffusion.

Differential Scanning Calorimetry
Differential scanning calorimetry (DSC) of drug was carried out by heating the sample from 100°C to 250°C at the heating rate of 10°C/min in a nitrogen environment. Thermograms obtained are shown in figure 9-11. DSC curve of the pure Metoprolol tartrate showed at 125°C (fig1) corresponds to the melting point of the drug. In the physical mixture of drug and polymer peak for drug and polymer was still observed at 127°C (fig2). The analysis of thermograms revealed no physical interaction between the drug and polymer.

**Table No.1 Composition of Immediate dose**

| INGREDIENTS         | QUANTITY (mg) |
|---------------------|---------------|
| Metoprolol tartrate | 20            |
| Soluble starch      | 5             |
| Polyvinylpyrrolidone| 4             |
| Lactose             | 63            |
| Magnesium stearate  | 5             |
| Talc                | 3             |

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Table No.2: Composition of sustained dose

| INGREDIENTS                        | BATCH CODES |
|------------------------------------|-------------|
|                                    | F1  | F2  | F3  | F4  | F5  | F6  | F7  | F8  | F9  |
| Metoprolol tartrate                | 50  | 50  | 50  | 50  | 50  | 50  | 50  | 50  | 50  |
| Hydroxypropylmethylcellulose K4000cp | 25  | 75  | 130 | 120 | 140 | 35  | 100 |
| Hydroxypropylmethylcellulose K15000cp | 180 | 100 | 100 | 40  | 30  | 25  | 150 | 120 |  - |
| Sodiumcarboxymethylcellulose       | 5   | 50  | 20  | 20  | -   | -   | 20  | 10  | 90  |
| Microcrystallinecellulose          | 30  | 30  | 30  | 30  | 30  | 30  | 30  | 30  | 30  |
| Lactose                            | 28  | -   | -   | 20  | 20  | 25  | -   | -   | -   |
| Sodium bicarbonate                 | 14  | 15  | 17  | 17  | 16  | 17  | 17  | 17  | 17  |
| Talc                               | 9   | 9   | 9   | 9   | 9   | 9   | 9   | 9   | 9   |
| Talc                               | 5   | 5   | 9   | 9   | 9   | 9   | 9   | 9   | 9   |

Table No.3 Evaluation and Characterization of powder.

| PARAMETER                      | BATCH CODE |
|--------------------------------|-------------|
|                                | F1  | F2  | F3  | F4  | F5  | F6  | F7  | F8  | F9  |
| Bulk density (g/cc)            | 0.48 | 0.52 | 0.42 | 0.46 | 0.57 | 0.52 | 0.44 | 0.42 | 0.46 |
| Tapped density (g/cc)          | 0.57 | 0.60 | 0.52 | 0.57 | 0.63 | 0.57 | 0.54 | 0.63 | 0.54 |
| Compressibility index (%)      | 18.75 | 13.33 | 119.2 | 19.29 | 9.52 | 8.77 | 18.05 | 30.15 | 14.81 |
| Hausner ratio                  | 1.08 | 1.15 | 1.23 | 1.23 | 1.10 | 1.09 | 1.22 | 1.50 | 1.19 |
| Angle of repose (Ø)            | 27.02 | 22.29 | 30.11 | 24.22 | 31.38 | 24.22 | 27.02 | 25.64 | 28.36 |
| %Weight variation              | 5.5  | 4.7  | 6.5  | 5.7  | 5.9  | 6.8  | 4.9  | 5.9  | 5.6  |
| % Friability                   | 0.11 | 0.13 | 0.11 | 0.12 | 0.12 | 0.14 | 0.13 | 0.11 | 0.13 |
| % Drug content                 | 98.3 | 98.75 | 99.28 | 98.13 | 97.86 | 99.12 | 98.45 | 98.11 | 97.25 |

Table No. 4 Percentages Cumulative Release

| Batch Code | 0.5Hr | 1Hr | 2Hr | 3Hr | 4Hr | 5Hr | 6Hr | 8Hr | 12Hr | Floating lag time |
|------------|-------|-----|-----|-----|-----|-----|-----|-----|------|-----------------|
| F1         | 21.68 | 27.34 | 33.54 | 38.46 | 42.16 | 48.58 | 58.68 | 69.52 | 74.4 | 87.68 | 42 |
| F2         | 21.95 | 29.65 | 35.84 | 41.62 | 49.82 | 57.40 | 63.46 | 70.42 | 77.9 | 86.40 | 48 |
| F3         | 22.40 | 30.14 | 39.0 | 47.23 | 53.92 | 61.20 | 69.74 | 76 | 80.7 | 84.41 | 45 |
| F4         | 22.45 | 31.5 | 37.23 | 43.92 | 54.23 | 61.33 | 68.1 | 73.98 | 79.25 | 84.20 | 35 |
| F5         | 24.23 | 33.42 | 38.99 | 45.92 | 51.23 | 56.9 | 61.92 | 69.1 | 75.26 | 87.18 | 40 |
| F6         | 25.31 | 32.85 | 39.1 | 47.25 | 55.36 | 63.87 | 68.93 | 77.29 | 84.66 | 92.16 | 45 |
| F7         | 26.45 | 37.12 | 46.25 | 54.62 | 62.20 | 68.32 | 73.5 | 79.92 | 84.05 | 94.32 | 48 |
| F8         | 25.40a | 29.92 | 36.88 | 44.23 | 52.00 | 57.89 | 63.42 | 70.25 | 76.93 | 92.30 | 35 |

Table No.5 Release exponent (n) values

| Release exponent (n) | Drug transport mechanism                  | Rate as a function of time |
|----------------------|-------------------------------------------|----------------------------|
| 0.5                  | Fickian diffusion (Case I transport)      | t^{0.5}                   |
| 0.5 < n < 1.0        | Anomalous transport (Non- Fickian diffusion) | t^{n-1}              |
| 1.0                  | Case-II transport                         | Zero order release        |
| > 1.0                | Super Case-II transport                   | t^{n-1}                   |
Table No.6 Correlation coefficient ($r^2$) of different kinetics model

| Formulation code | Zero order kinetic | First order kinetic | Higuchi’s square root kinetic | Korsemeyer equation kinetic |
|------------------|--------------------|---------------------|-------------------------------|----------------------------|
| F1               | 0.9712             | 0.853               | $R^2 = 0.971$                 | 0.961                      |
| F2               | 0.9775             | 0.929               | $R^2 = 0.977$                 | 0.989                      |
| F3               | 0.9656             | 0.983               | $R^2 = 0.965$                 | 0.990                      |
| F4               | 0.966              | 0.979               | $R^2 = 0.966$                 | 0.988                      |
| F5               | 0.9553             | 0.891               | $R^2 = 0.955$                 | 0.987                      |
| F6               | 0.9717             | 0.909               | $R^2 = 0.971$                 | 0.991                      |
| F7               | 0.9440             | 0.892               | $R^2 = 0.944$                 | 0.992                      |
| F8               | 0.9661             | 0.812               | $R^2 = 0.966$                 | 0.988                      |
| F9               | 0.9366             | 0.932               | $R^2 = 0.936$                 | 0.985                      |

Figure 1:- DSC thermograms of Metoprolol tartrate

Fig. 2:- DSC thermograms of formulation
Summary & Conclusion

The preparation was found to follow the Fickian transport. The data were fitted to Korsemeyer’s equation, F6; F7 (Table No. 6) formulation showed linearity with exponent value (n) ranging 0.34, 0.31 and R² found to be 0.991 and 0.992. The overall result of the present work shows that Metoprolol tartrate oral bioavailability which has been reported to be ~50%, due to rapid hepatic first-pass metabolism and because MT undergoes degradation in the colon. If the MT dosage form can be retained in the stomach as long as possible, to allow for maximum absorption, MT’s bioavailability could be improved. Gastric floating drug delivery is one approach; in it, the GI residence time was prolonged because of the floating behavior. Different grades of HPMC (K4M and K15M) and SCMC were used as swellable polymers. The reason behind choosing HPMC polymer was its low-density hydrocolloid system which upon contact with water form hydrogel layer which act as a gel boundary for the delivery system, but it would fail to retard the release of drug through the matrix because of its solubility in stomach pH. Various grades of HPMC were reported to have duration of buoyancy of more than 8 hours in the simulated meal medium, as well as in distilled water. SCMC was used in combination with HPMC to slow the drug release; SCMC’s ability to do this may be due to low solubility of SCMC at pH 1.2 to 3. Our focus was on the floatability of the dosage form, so the HPMC concentration was increased throughout the experimental design. Different viscosity grades of HPMC show good floatability.

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