The objective of the present investigation is formulation development and evaluation of floating tablets of two drugs namely (i) lornoxicam and (ii) diltiazem employing a new modified starch namely cross-linked starch-urea. Floating tablet formulation of the selected two drugs was optimized by 2^3 factorial design in the present study. Sustained release floating tablets of (i) lornoxicam (a poorly water soluble drug) and (ii) diltiazem hydrochloride (a highly water soluble drug) were formulated employing cross-linked starch-urea, a new modified starch (50%) as matrix forming polymer, sodium bicarbonate as gas generating agent, beeswax and ethyl cellulose as floating enhancers. Sustained release of the two selected drugs over 10-12 h is aimed in addition to good floating characteristics. Formulation of floating tablets in each case was optimized by 2^3 factorial design.

The specific objectives of the investigation include formulation and evaluation of floating tablets of (i) lornoxicam and (ii) diltiazem employing a new modified starch, cross-linked starch-urea as matrix forming polymer, sodium bicarbonate as gas generating agent, beeswax and ethyl cellulose as floating enhancers; to evaluate the individual and combined (or interaction) of formulation variable involved on floating and drug release characteristics of floating tablets in a 2^3 factorial study in each case; optimization of floating tablet by 2^3 factorial design to achieve a floating lag time of 15-20 sec; to develop polynomial equation describing the relationship between the response, floating lag time (Y) and the three variables, level of sodium bicarbonate (X_1), level of beeswax (X_2) and level of ethyl cellulose (X_3) based on the observed
results and to develop optimized floating tablet formulations based on the polynomial equation in each case; to evaluate the kinetics and mechanism of drug release from the floating tablets prepared; to evaluate the stability of optimized floating tablet formulations developed as per ICH guidelines and pharmacokinetic evaluation of optimized floating tablet formulations developed in rabbits.

Matrix tablets each containing 8 mg of lornoxicam were formulated employing Cross-linked starch-urea (50%) as matrix forming polymer, sodium bicarbonate as gas generating agent and ethyl cellulose and beeswax as floating enhancers. Lornoxicam floating tablets were formulated as per 2<sup>3</sup> factorial design. The three factors involved in the 2<sup>3</sup> factorial study are sodium bicarbonate (Factor A), beeswax (Factor B) and ethyl cellulose (Factor C). The two levels of sodium bicarbonate (Factor A) are 10 and 20%, the two levels of beeswax (Factor B) are 2% and 5% and the two levels of ethyl cellulose (Factor C) are 5% and 10%. Eight lornoxicam floating tablet formulations were prepared employing selected combinations of the levels of the three factors as per 2<sup>3</sup> factorial design. The floating tablets were prepared by melting-wet granulation method and were evaluated for drug content, hardness, friability, disintegration time, floating lag time, floating time and drug release characteristics.

From the results obtained the following conclusions are drawn.

1. Lornoxicam floating tablets prepared as per 2<sup>3</sup> factorial design were non-disintegrating in water and aqueous acidic (pH 1.2) and alkaline (pH 7.4) fluids and were of good quality with regard to drug content, hardness, friability and suitable for controlled release.
2. The individual effects of sodium bicarbonate (Factor A) and beeswax (Factor B) and their combined effect (AB) on the floating lag time were highly significant (P < 0.01). Whereas the individual effect of ethyl cellulose (Factor C) and combined effects of sodium bicarbonate and ethyl cellulose (AC) and beeswax and ethyl cellulose (BC) were not significant in influencing floating lag time of the tablets.

3. Formulations $F_{ab}$, $F_{ac}$ and $F_{abc}$ exhibited excellent floating over 12-15 h with a floating lag time in the range 30-35 seconds. Higher levels (20%) of sodium bicarbonate gave shorter floating lag time.

4. Lornoxicam release from the floating tablets prepared was slow and spread over more than 12 h and dependent on the composition of the tablets.

5. The order of increasing release rate ($K_1$) observed with various formulations was $F_a > F_{1} > F_{ac} > F_{c} > F_{bc} > F_{b} > F_{abc} > F_{ab}$.

6. Lornoxicam release from the floating tablets was by non-Fickian diffusion mechanism in all the cases except $F_a$ that gave rapid release of drug Fickian diffusion was the drug release mechanism.

7. Optimization of lornoxicam floating tablet formulation was done taking floating lag time as the parameter for optimization. For optimization, floating lag time was taken as response ($Y$) and level of sodium bicarbonate as ($X_1$), level of beeswax as ($X_2$) and level of ethyl cellulose as ($X_3$).

8. The polynomial equation describing the relationship between the response, $Y$ and the variables, $X_1$, $X_2$ and $X_3$ based on the observed data was found to be $Y = 11.59 - 11.18 (X_1) + 4.36 (X_2) - 4.37 (X_1X_2) - 1.08 (X_3) + 0.895 (X_1X_3) - 0.735 (X_2X_3) + 0.79 (X_1X_2X_3)$.

9. Based on the polynomial equation developed, the optimized lornoxicam floating tablet formulation with a floating lag time of 15 seconds or 0.25 min could be
Matrix tablets each containing 60 mg of diltiazem hydrochloride were formulated employing Cross linked starch-urea (50%) as matrix forming polymer, sodium bicarbonate as gas generating agent and ethyl cellulose and beeswax as floating enhancers. Diltiazem floating tablets were formulated as per 2³ factorial design. The three factors involved in the 2³ factorial study are sodium bicarbonate (Factor A), beeswax (Factor B) and ethyl cellulose (Factor C). The two levels of sodium bicarbonate (Factor A) are 10 and 20 %, the two levels of beeswax (Factor B) are 2 % and 5 % and the two levels of ethyl cellulose (Factor C) are 5% and 10%. Eight diltiazem floating tablet formulations were prepared employing selected combinations of the levels of the three factors as per 2³ factorial design. The floating tablets were prepared by melting-wet granulation method and were evaluated for drug content, hardness, friability, disintegration time, floating lag time, floating time and drug release characteristics. From the results obtained the following conclusions are drawn.
1. Diltiazem floating tablets prepared as per 2 3 factorial design were non-disintegrating in water and aqueous acidic (pH 1.2) and alkaline (pH 7.4) fluids and were of good quality with regard to drug content, hardness, friability and suitable for controlled release.

2. The individual effects of sodium bicarbonate (Factor A) and ethyl cellulose (Factor C) and their combined effect (AC) on the floating lag time were significant (P < 0.05). Whereas the individual effect of bees wax (Factor B) and all other combined effects of the three factors involved were not significant in influencing floating lag time of the tablets.

3. Formulations F_a, F_ac and F_abc exhibited excellent floating over 12-14 h with a floating lag time in the range 15-32 seconds. Higher levels (20%) of sodium bicarbonate gave shorter floating lag time.

4. Diltiazem release from the floating tablets prepared except formulation F_a was slow and spread over 12 h and dependent on the composition of the tablets. Drug release from formulation F_a was very rapid.

5. Diltiazem release from the floating tablets was by non-fickian diffusion mechanism in all the cases except F_a. In the case of formulation F_a that gave rapid release of drug fickian diffusion was the drug release mechanism.

6. Optimization of diltiazem floating tablet formulation was done taking floating lag time as the parameter for optimization. For optimization, floating lag time was taken as response (Y) and level of sodium bicarbonate as (X_1), level of bees wax as (X_2) and level of ethyl cellulose as (X_3).

7. The polynomial equation describing the relationship between the response, Y and the variables, X_1, X_2 and X_3 based on the observed data was found to be

\[ Y = 6.126 - \]
Based on the polynomial equation developed, the optimized diltiazem floating tablet formulation with a floating lag time of 20 seconds or 0.33 min could be formulated employing sodium bicarbonate (100mg/tablet), beeswax (17.5mg/tablet) and ethyl cellulose (37.5mg/tablet).

The optimized formulation ($F_{opt}$) exhibited a floating time of 14 h with a lag time of 22 seconds fulfilling the target floating lag time set indicating validity of the optimization technique employed.

Formulations $F_{opt}$ and $F_{ac}$ prepared exhibited excellent floating characteristics (floating over 13–14 h with a lag time of 22 and 30 seconds respectively) and good sustained release of diltiazem over 12 h.

Formulations $F_{opt}$ and $F_{ac}$ are considered as the best floating tablet formulations of diltiazem suitable for b.i.d administration.

The stability of optimized Floating Tablet formulations of (i) Lornoxicam (ii) Diltiazem developed was tested as per ICH guidelines. The FTs were taken in HDPE bottles and were stored at 40°C ± 2°C and at 75% RH for 6 months.

The products were then tested for drug content, floating and drug release properties. The difference in the percent drug content before and after storage was not significant ($P>0.05$). No difference was also observed in the floating characteristics of the FTs tested before and after storage. The release profiles of the FTs tested remained unchanged during the storage period. The similarity of the drug release profiles before and after storage in each case was tested by difference factor ($f_1$) and similarity factor ($f_2$). The $f_1$ and $f_2$ were 3.89 and 79.13 respectively in the case of Lornoxicam FTs and 1.55 and 85.85 in the case of Diltiazem FTs. These values indicate that the drug release profiles...
before and after storage are similar in each case. Thus the drug release characteristics of the optimized floating tablet formulations of (i) Lornoxicam and (ii) Diltiazem remained unchanged during stability testing.

Pharmacokinetic evaluation was done on optimized lornoxicam floating tablet formulation in comparison to its immediate release tablets in healthy rabbits to assess their in vivo performance. From the results obtained the following conclusions are drawn.

1. Lornoxicam was absorbed rapidly from IR tablets with an absorption rate constant ($k_a$) of 2.30 $h^{-1}$. A $C_{max}$ of 1.2±0.09 µg/ml was observed at 1h following oral administration of lornoxicam IR tablets. Plasma concentration were later decreased rapidly.

2. Lornoxicam from the FTs was absorbed slowly with a $k_a$ of 0.730 $h^{-1}$. A $C_{max}$ of 0.70±0.04 µg/ml at 3h was observed with FTs.

3. The plasma drug concentrations were sustained within a narrow range for extended period of time in the case of FTs.

4. The MRT was increased for 3.92 h for lornoxicam IR tablets to 5.53 h with FTs indicating longer stay of the drug in the body when administered as FTs compared to IR Tablets.

5. Based on (AUC)$_{0-\alpha}$, the relative bioavailability (BA) of lornoxicam from FTs was 117.0 % when compared to lornoxicam IR tablets (100%). Thus, the results of in vivo studies indicate that lornoxicam was absorbed slowly from FTs and the plasma drug concentrations were sustained over longer period of
time when compared to IR tablets. FTs also exhibited longer MRT and higher bioavailability when compared to IR tablets.

**INNOVATIVENESS OF THE WORK:**

The present investigation resulted in the development of floating tablets of two drugs namely (i) lornoxicam and (ii) diltiazem on a rational basis employing optimization by $2^3$ factorial designs. The innovativeness of the research work is the use of optimization technique and factorial designs in the development of floating tablets. The application of optimization techniques in pharmaceutical product development is relatively new and these techniques are very essential for QbD approach, which is advocated by regulating agencies globally in pharmaceutical product development in recent years.