Formulation and Evaluation of Lamivudine Floating Tablets by Sublimation Method

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ABSTRACT

The objective of the study was to develop an oral controlled release drug delivery system of Lamivudine using the sublimation method. Camphor was used as the sublimation material to prepare gastro retentive tablets that are low-density and easily floatable. Camphor was changed to pores in the tablet during the sublimation process. Floating properties of tablets and tablet density were affected by the sublimation of camphor. Release profiles of the drug from the gastro retentive tablets were affected by tablet density/porosity. The effects of different formulation variables HPMC and the effects of different concentrations were studied. The in vitro evaluation was carried out and it was found that the drug release was affected by different concentrations of polymers used. The highest percentage of drug release (96.89±0.83) was observed with xanthan polymer and followed diffusion with erosion mechanism (Non-Fickian transport).

Keywords: Lamivudine, floating, HPMC K4M, Xanthan, Camphor, Non-Fickian transport.
INTRODUCTION

Despite tremendous advancements in drug delivery, the oral route remains the preferred route for the administration of the therapeutic agents because of the low cost of the therapy and ease of administration lead to high levels of patient compliance. Conventional oral dosage forms provide a specific drug concentration in systemic circulation without offering any control over drug delivery. Thus, the oral administration of a medication employing controlled release drug delivery system (CRDDS) should ideally enable the drug release at a predetermined, predictable and controlled rate to obtain the required plasma levels and to keep them steady for a prolonged period. An important requisite for the successful performance of oral CRDDS is that the drug should have good absorption throughout the GIT, preferably by passive diffusion, to ensure continuous absorption of the released drug. A major constraint in oral controlled drug delivery is that not all drug candidates are absorbed uniformly throughout the GIT. Some drugs are absorbed in a particular portion of the GIT. Such drugs are said to have an absorption window, which identifies the drug’s primary region of absorption in the GIT. An absorption window exists because of physiological, physic-chemical, or biochemical factors. Because most drugs are absorbed by passive diffusion of the un-ionizes form, the extent of ionization at various pH levels can lead to non-uniform absorption or an absorption window the presence of certain enzymes in a particular region of the GIT also can lead to regional variability in the absorption of drugs that are substrates of those enzymes. All these above limitations could be overcome, for various selectively selected drugs, by prolonging the gastric residence time of the pharmaceutical dosage form i.e., the development of gastroretentive drug delivery systems. Dosage forms that can be retained in the stomach for a prolonged and predictable period are called GRDDS. Therefore the real issue in the development of oral GRDDS is not just to prolong the delivery of drugs for 12 hours or more but to prolong the presence of DDS in the stomach or upper GI tract until the entire drug is released. Thus, GRDDS can improve the controlled delivery of drugs that have an absorption window by continuously releasing the drug for a prolonged time before it reaches its absorption site, thus ensuring its optimal bioavailability. These systems incorporate hydrophilic polymers like HPMC K4M, Xanthan gum, a sublimating agent like Camphor, a filler like Lactose, Anti adherent like Talc and Lubricant like Magnesium stearate are incorporated in the tablet.

MATERIALS AND METHOD

Materials

Lamivudine was received as a generous gift sample from Aurbindo Labs, Hyderabad. HPMC K4 was available from Signet chemical corporation, Mumbai. Xanthan gum from Lucid...
pharmaceuticals, Hyderabad. Camphor from Desmo Exports Limited, Mumbai. Magnesium Stearate and Talc from S. D. Fine Chemicals, Mumbai. Lactose from Delta Chemsol, Mumbai. All the chemicals used are pharmaceutical grade.

**Methods**

**Preparation of floating tablets:**

Lamivudine tablets were prepared by direct compression method. Accurately weighed quantities of polymer and lactose were taken in a motor and mixed geometrically, to this required quantity of LAM was added and mixed then passed through sieve # 40. To this mixture magnesium stearate was added and mixed for 5 minutes, later talc was added and mixed for 2 minutes, to this add solid inert Camphor and the mixture equivalent to 250 mg was compressed into tablets with 8mm round concave punches at a hardness of 4-5 kg/cm². After compression, the tablets were subjected to sublimation at 60⁰C for 2 hr in a vacuum oven. This results in a porous formation on the tablets which helps in floating.

| F. Code | HPMC K4M | Xanthan Gum | Camphor | Magnesium Stearate | Talc | Lactose | Total Weight |
|---------|----------|-------------|---------|--------------------|------|---------|-------------|
| F1      | 95       | --          | 30      | 5                  | 5    | 15      | 150         |
| F2      | 85       | --          | 20      | 5                  | 5    | 35      | 150         |
| F3      | 75       | --          | 10      | 5                  | 5    | 55      | 150         |
| F4      | 65       | --          | 8       | 5                  | 5    | 67      | 150         |
| F5      | 55       | --          | 6       | 5                  | 5    | 79      | 150         |
| F6      | --       | 95          | 30      | 5                  | 5    | 15      | 150         |
| F7      | --       | 85          | 20      | 5                  | 5    | 35      | 150         |
| F8      | --       | 75          | 10      | 5                  | 5    | 55      | 150         |
| F9      | --       | 65          | 8       | 5                  | 5    | 67      | 150         |
| F10     | --       | 55          | 6       | 5                  | 5    | 79      | 150         |

Weight of Lamivudine – 100mg; The average weight of all the formulations was 250mg

**Evaluation of Floating Tablets** \(^{(10,11)}\)

**In vitro buoyancy studies**

The duration of time for which the dosage form constantly remained on the surface of the medium was determined as the total floating time.

**Weight variation test**

Twenty (20) tablets from each batch were individually weighed in grams on an analytical balance. The average weight and standard deviation were calculated, the individual weight of each tablet was also calculated using the same and compared with average weight.

**Thickness test**
The thickness in millimeters (mm) was measured individually for 10 pre-weighed tablets by using vernier calipers. The average thickness and standard deviation were reported.

**Hardness test**

Tablet hardness was measured using Pfizer hardness tester. The crushing strength of the 10 tablets with known weight and thickness of each was recorded in kg/cm² and the average hardness, and the standard deviation was reported.

**Friability test**

Twenty (20) tablets were selected from each batch and weighed. Each group of tablets was rotated at 25 rpm for 4 minutes (100 rotations) in the Roche friabilator. The tablets were then dedusted and re-weighed to determine the loss in weight. Friability was then calculated as per weight loss from the original tablets.

**Drug content**

Twenty (20) tablets were taken, powdered and the powder equivalent to one dose was transferred to 100 ml volumetric flask, and 0.1N HCl was added. The volume was then made up to the mark with 0.1N HCl. The solution was filtered and diluted suitably and drug content in the samples was estimated using a UV-Visible spectrophotometer at λmax 285 nm.

**In vitro swelling index**

The tablets from each batch were weighed and placed in a beaker containing 200 mL 0.1N HCl of pH 1.2. After each hour the tablets were removed from the beaker and weighed again up to 12 hours.

Swelling index (S.I) = (Wt-Wo)/ Wo x 100,

Wt = weight of tablet at time t hour,

Wo = weight of the tablet before immersion

**In vitro drug release studies**

The in vitro drug release study was performed for all the tablets using the USP Type II dissolution apparatus using 900ml of 0.1NHCl as a dissolution medium at 37⁰C at 50 rpm. At predetermined time intervals samples (5 mL) were collected and replenished with the same volume of fresh medium. The drug content in the samples was estimated using a UV-Visible spectrophotometer a λmax 285 nm.

**Selection of optimized formulations based on release kinetic modeling**

There are a number of kinetic models, which described the overall release of drug from the dosage forms. Because qualitative and quantitative changes in a formulation may alter drug release and in vivo performance, developing tools that facilitate product development by reducing the necessity
of bio-studies is always desirable. In this regard, the use of \textit{in vitro} drug dissolution data to predict \textit{in vivo} bio-performance can be considered as the rational development of controlled release formulations. So, the method of approach to investigate the kinetics of drug release from controlled release formulation was carried out by Model dependent methods (zero order, first order, Higuchi, Korsmeyer-Peppas model, Hixson Crowell, Baker-Lonsdale model, Weibull model, etc.)

RESULTS AND DISCUSSION

Preformulation Studies

Drug-excipient compatibility studies by FTIR studies

FT-IR spectroscopic studies were conducted to determine possible drug-polymer interactions. IR spectra of pure drug Lamivudine (LAM), HPMC K4M, Xanthan gum (XAN), Camphor (CAM), and physical mixture of Lamivudine and polymers were obtained which shows all the characteristic peaks (table 2) and indicates that there is no interaction between drug and the polymers, which confirms the stability of the drug.

DISCUSSION

Lamivudine is highly soluble in 0.1N HCl, having quantitative solubility 276.08 mg/mL. The bulk density (0.49-0.51 g/cc) Hausner's ratio (1.08-1.18) and compressibility index (22.1-25.5) of all the formulations were confirmed the good flow property (Table.3). The total weight of each formulation was maintained constant, the weight variation of the tablet was within the permissible limits of 75\%, as specified for tablet weighing 130-324 mg. weight of the tablet was fixed at 250mg and the weight variation for every batch was tested and found in the acceptance limits (Table. 3). The weight of the formulations ranged from 248±1.5 to 252±1.7. These values are within the acceptable limits (Table.3). The thickness of floating tablets ranged from 4.48±0.07 to 4.86±0.3mm and linearly correlated with the weight of the tablets. The hardness of the tablet was fixed 5.5kg/cm² and was maintained for all the batches to minimize the effect of hardness on the drug release. Friability range varied from 0.21 to 0.5, confirm with normal range. The content uniformity was found to be in the range of 96.33\% to 98.56\%. This signifies the drug content uniformity of the formulation results were present in (Table.3). All formulations were tested for \textit{in vitro} drug release. The optimized formulations among HPMC K4M and Xanthan gum are F4 and F8. Formulations subjected to curve fitting analysis showed that the formulations best fit for zero-order release with diffusion and erosion mechanism. The formulation F8 showed a high regression value of 0.97 for zero-order and 0.92 for Higuchi order with complete drug release in 12 hrs made it to select as an optimized formulation compared with other formulations.
Table 2: FTIR Spectra studies

|          | LAM          | CAM          | LAM+HPMCK4+CAM | LAM+XAN+CAM |
|----------|--------------|--------------|---------------|-------------|
| CH3      | 1487.99 cm⁻¹ | 1447.99 cm⁻¹ | 14530.08 cm⁻¹ | 1450.21 cm⁻¹ |
| C=O      | 1650.25 cm⁻¹ | 1738.00 cm⁻¹ | 1738.57 cm⁻¹ | 1737.75 cm⁻¹ |
| C=N      | 1607.34 cm⁻¹ | ----         | 1611.75 cm⁻¹ | 1607.47 cm⁻¹ |

Table 3: Physical properties of Pre-compressed granules.

| F.Code | CI (%) | Bulk density (g/cc) | Tapped density (g/cc) | Angle of repose (°) | Hausner’s ratio |
|--------|--------|---------------------|-----------------------|---------------------|-----------------|
| F1     | 22.1   | 0.48                | 0.56                  | 27.70              | 1.15            |
| F2     | 25.8   | 0.49                | 0.65                  | 26.50              | 1.13            |
| F3     | 22.5   | 0.48                | 0.64                  | 29.20              | 1.18            |
| F4     | 25.4   | 0.50                | 0.58                  | 28.40              | 1.17            |
| F5     | 22.3   | 0.51                | 0.59                  | 29.50              | 1.15            |
| F6     | 22.2   | 0.48                | 0.66                  | 28.40              | 1.18            |
| F7     | 23.7   | 0.49                | 0.62                  | 29.80              | 1.08            |
| F8     | 22.2   | 0.49                | 0.59                  | 27.50              | 1.18            |
| F9     | 24.8   | 0.49                | 0.58                  | 29.40              | 1.14            |
| F10    | 25.3   | 0.50                | 0.62                  | 28.60              | 1.16            |

Table 4: Post compression parameters.

| F.code | Weight variation (mg)ᵃ | Hardness (kg/cm²)ᵇ | Thickness (mm) | Friability (%) | Drug content (%)ᶜ |
|--------|------------------------|--------------------|---------------|---------------|-------------------|
| F1     | 252±1.3                | 5.5±0.5            | 4.76±0.06     | 0.23          | 98.56±1.2        |
| F2     | 250±1.1                | 5.6±0.3            | 4.86±0.03     | 0.48          | 98.21±1.6        |
| F3     | 248±1.5                | 5.4±0.5            | 4.76±0.04     | 0.51          | 97.91±1.5        |
| F4     | 252±1.3                | 5.5±0.2            | 4.63±0.06     | 0.22          | 97.75±1.6        |
| F5     | 251±0.8                | 5.4±0.5            | 4.68±0.05     | 0.35          | 97.48±1.4        |
| F6     | 249±0.8                | 5.1±0.2            | 4.55±0.25     | 0.38          | 97.69±1.3        |
| F7     | 259±1.7                | 5.5±0.5            | 4.5±0.04      | 0.41          | 97.35±1.6        |
| F8     | 249±0.8                | 5.5±0.3            | 4.62±0.07     | 0.29          | 96.55±1.4        |
| F9     | 250±1.7                | 5.7±0              | 4.56±0.07     | 0.25          | 97.41±1.2        |
| F10    | 248±1.5                | 5.9±0.1            | 4.48±0.04     | 0.28          | 97.97±1.2        |

Mean ± SD : a n=3, b n=3, c n=3.

Table 5: Floating properties of prepared tablets.

| Formulation | Floating time (hr) |
|-------------|--------------------|
| F1          | >12                |
| F2          | >12                |
| F3          | 8                  |
| F4          | >12                |
| F5          | 10                 |
| F6          | >12                |
| F7          | >12                |
| F8          | >12                |
| F9          | 10                 |
| F10         | >12                |
Figure 1: Pictorial representation of buoyancy of tablets for 12 hr

Table 6: *In vitro* swelling index

| Formulation | Swelling index |
|-------------|----------------|
| F1          | 35.16±2.12     |
| F2          | 36.61±1.96     |
| F3          | 40.17±1.23     |
| F4          | 36.75±1.98     |
| F5          | 38.21±1.79     |
| F6          | 37.12±1.79     |
| F7          | 42.23±1.98     |
| F8          | 39.12±1.23     |
| F9          | 36.89±1.96     |
| F10         | 42.36±1.98     |

Figure 2: *In vitro* release of Lamivudine from formulations [F1-F5]
SUMMARY AND CONCLUSION

Lamivudine floating tablets were successfully prepared with hydrophilic polymers like HPMC K4M and Xanthan gum. Floating properties of tablets and tablet density were affected by the sublimation of camphor. Prepared floating gastroretentive tablets had no floating lag time. All formulations were tested for buoyancy properties i.e. total floating time and swelling index. Almost all the formulations showed satisfactory results. Formulation F3 and F5 show less floating time with HPMC K4, F9 with Xanthan gum when compared with other formulations and swelling studies are also showed satisfactory results. The optimized formulations among HPMC K4M and Xanthan gum are F4 and F8 and were best fitted to Zero-order kinetics and follow diffusion and erosion mechanism. The formulation F8 showed a high regression value of 0.97 for Zero-order and 0.92 for Higuchi order with complete drug release in 12 hrs. Drug-excipients interaction of optimized formulations was carried out by using FTIR studies. In this analysis, drug-excipient interactions were not observed.

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Table 7: Correlation coefficient (R²) of different kinetic models for optimized formulation

| Formulation | % Drug release | Time (min) | Zero order | First order | Higuchi | Korsemeyer peppas | n value |
|-------------|----------------|------------|------------|------------|---------|------------------|---------|
| F8          | 98.89          | 12hr       | 0.97       | 0.68       | 0.92    | 0.83             | 0.58    |

*Each value represents the mean ± SD (n=3)
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