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RESEARCH ARTICLE

Formulation and Evaluation of Gastroretentive Floating Dosage Form of Lamivudine

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ABSTRACT

Introduction: Formulation of potent drug molecules as dosage form still draws continuous interest and challenges against its optimization toward pharmacokinetics parameters such as absorption, bioavailability, onset of action, and duration of action. **Material:** The consistent maintenance of plasma drug concentration within the therapeutic level for prolonged periods of time has been persisting as a challenge to the pharmaceutical field. Method: The conventional dosage forms are designed to be consumed by the patients two, three, or even 4 time a day, which ultimately results in non-compliance by the patient. **Result:** In accordance with the therapeutic objective, to design and evaluate hydrodynamically balanced non-effervescent floating drug delivery systems of lamivudine as controlled release modules, which prolongs the release rate of the drug while extending the residence time of the drug within the body environment and without causing undeliterious effects to the subject. **Conclusion:** The drugs with low biological half-life and unstable in the small intestine are good candidates for Gastroretentive dosage forms.

Keywords: Gastroretentive, lamivudine, floating dosage forms

INTRODUCTION

The Origins of "Controlled" Drug Delivery

In the mid-1960s, Judah Folkman, MD, at Harvard was circulating rabbit blood inside a Silastic® (silicone rubber) arteriovenous shunt and discovered that if he exposed the tubing to anesthetic gases on the outside, the rabbits would fall asleep. He proposed that short, sealed segments of such tubing containing a drug could be implanted, and if the silicone did not change in dimensions or composition, the implant would become a constant rate drug delivery device. He also showed that the rate decreased as the tubing thickness increased, which is obvious today, but back then it was the first suggestion of a zero-order controlled drug delivery (CDD) implant *in vivo*. Meanwhile, across the country in Palo Alto CA, Alejandro ("Alex") Zaffaroni, an outstanding synthetic drug chemist and entrepreneur, had been thinking about the concept of zero-order delivery and controlled delivery devices. He founded a company in the late 1960s focused on the concept of CDD. He called it Alza, after the first two letters of his first and last names.[1-4]

Different Types of Controlled Release Systems

For conventional formulations, the plasma concentration of a drug is directly proportional to the administrated dose [Figure 1], displays the typical profiles of plasma drug concentration as a function of time after oral or intravenous administration. Those formulations are difficult to maintain the therapeutic dose for extended periods of time, which usually require multiple administrations to obtain therapeutic effect. In addition, systemic

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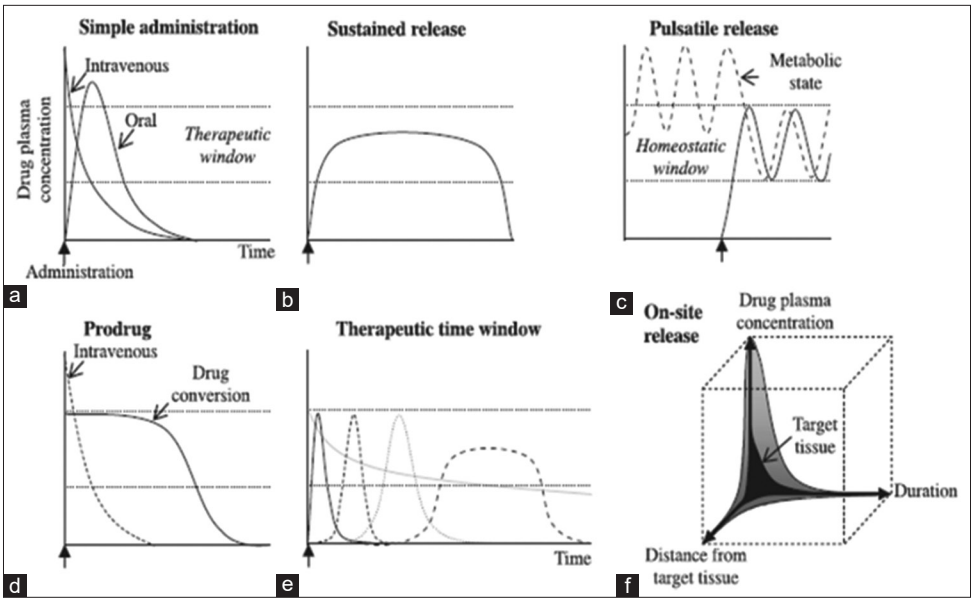


Figure 1: Different types of controlled release systems. (a) Drug delivery based on simple diffusion and partition. (b) Sustained release to prolong the therapeutic period. (c) Pulsatile release to tightly maintain homeostasis. (d) Release profile and drug conversion of the polymer drug conjugate as a prodrug. (e) Temporally controlled (or sequential) release profile of multiple drugs. (f) Onsite release to maximize therapeutic efficiency and to minimize side effect

circulation of high drug concentration often induces the adverse effect, because in this case, drug delivery solely depends on simple diffusion or partition from blood stream to target site. Only one advantage of conventional formulations is that the cost of development is low [Figure 1].

Gastroretentive Drug Delivery Systems (GRDDS)[5]

Dosage forms that can be retained in the stomach are called GRDDS. GRDDS can improve controlled delivery of drugs with an absorption window by continuously releasing the drug for a prolonged period before it reaches its absorption site, thus ensuring optimal bioavailability. Drugs with a narrow absorption window are mostly associated with improved absorption at the jejunum and ileum due to the enhanced absorption properties of these sites (e.g. large surface area), or because of enhanced solubility in the stomach as opposed to the more distal parts of the gastrointestinal tract (GIT) [Figure 2].

Factors Controlling Gastric Retention of Dosage Forms[6]

The gastric retention time (GRT) of dosage forms is controlled by several factors such as density and

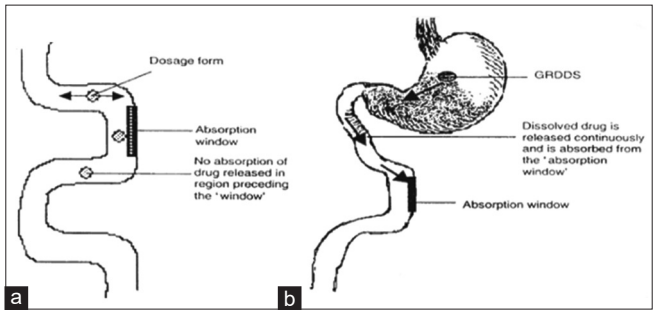


Figure 2: Drug absorption in (a) conventional dosage forms and (b) gastroretentive drug delivery systems

size of the dosage form, food intake, nature of the food, posture, age, sex, sleep, and disease state of the individual (e.g, gastrointestinal diseases and diabetes) and administration of drugs such as prokinetic agents (cisapride and metoclopramide).

Floating Systems

Floating drug delivery systems (FDDSs) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time [Figure 3]. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach.

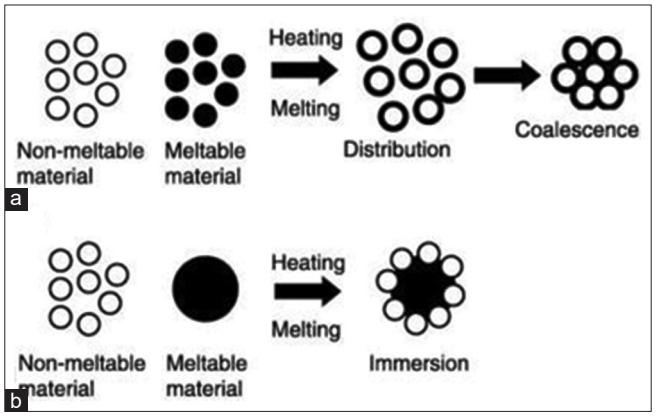


Figure 3: Modes of melt agglomeration: (a) Distribution and (b) immersion

This results in an increased GRT and a better control of the fluctuations in plasma drug concentration.[7-15]

Melt Granulation

Melt granulation or pelletization is a one-step process allowing the transformation of a powder mix (containing the drug) into granules or spheronized pellets. The technique necessitates high shear mixing in the presence of a meltable binder which may be sprayed in molten state onto the powder mix as in classic wet granulation process. This is referred to as "pump-on" technique. Alternatively, the binder may be blended with the powder mix in its solid or semi-solid state and allowed to melt (partially or completely) by the heat generated from the friction of particles during high shear mixing referred to "melt-in" process. The melted binder forms liquid bridges with the powder particles that shape into small agglomerates (granules) which can by further mixing under controlled conditions transform to spheronized pellets.

Melt granulation is one of the most applied processing techniques in the array of pharmaceutical manufacturing operations. Melt granulation process is currently applied in the pharmaceutical manufacturing operations for manufacture of variety of dosage forms and formulations such as immediate release pellets, granules, and tablets.

Modes of Melt Granulation

Materials used in melt granulation[5,6,16-23]

Lipids are considered as an alternative to polymer in the design of sustained drug delivery systems due to their advantages such as the low melt viscosity (thus avoiding the need of organic solvents for solubilization) absence of toxic impurities such as residual monomer catalysis and initiators, potential biocompatibility, and biodegradability. The various meltable binders for the sustained drug delivery mentioned in Tables 1 and 2.

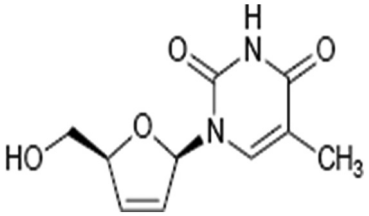
Drug Profile and Polymer Profile

Drug profile

Lamivudine Description: White, amorphous powder and hygroscopic

Category: Antiretroviral, reverse transcriptase inhibitor (nucleoside)

Structure:



Chemical name: 1-((2R, 5S)-5-(hydroxymethyl)-2, 5-dihydrofuran-2-yl) - 5- methylpyrimidine-2, 4(1H, 3H)-dione

Table 1: Hydrophilic meltable binders in the melt granulation technique

Hydrophilic meltable binder	Typical melting range (°C)
Gelucire 50/13	44–50
Poloxamer 188	50.9
Polyethylene glycol 2000	42–53
3000	48–63
6000	49–63
8000	54–63
10,000	57–64
20,000	53–66
Stearate 6000 WL1644	46–58

Table 2: Hydrophobic meltable binders in the melt granulation technique

Hydrophobic meltable binder	Typical melting range (°C)
Beeswax	56–60
Carnauba wax	75–83
Cetyl palmitate	47–50
Glyceryl behenate	67–75
Glyceryl monostearate	47–63
Glyceryl palmitostearate	48–57
Glyceryl stearate	54–63
Hydrogenated castor oil	62–86
Microcrystalline wax	58–72
Paraffin wax	47–65

Molecular formula: $C_{10} H_{12} N_2 O_4$
Molecular weight: 224.2
Solubility: Soluble in water and sparingly soluble in ethanol (95%)
Storage: Store in a well-closed container, protected from light
Specific rotation: Between −39.0° and −46.0°, determined in a 0.7% W/V solution in water.
Sulfated ash: Not more than 0.3%
Loss on drying: Not more than 20 ppm, determined on 1.0 g by drying at 105° for 3 h.

Polymer profile

Hydroxypropyl methylcellulose (HPMC)
Name: HPMC, Chemical name: Cellulose, 2-hydroxylpropylmethyl ether Common name: Methocel, hypromellose
Appearance: White or off-white power with odorless and tasteless.
Carbonation temperature: 280–300°C.
Solubility: Dissolves in water, some organic solvents or some water organic components. Hardly dissolves in waterless ethanol, ether, or acetone. Expands to clear or slightly muddy colloid solution in cold water.
Apparent density: 0.25–0.70 g/cm^3
Specific gravity: 1.26–1.31.
Applications: Suspending agent, viscosity modifier, film, and matrix forming material, tablet binder, and adhesive ointment ingredient.
Stability: It is very stable in dry condition from pH 3.0 to 11.0. Aqueous solutions are liable to be affected by microorganisms. It has attracted significant attention for drug delivery applications. It remains glossy in dehydrated state and swollen in the presence of water to form an elastic gel. It is categorized under the class "hydrogels." It is soluble in cold water, insoluble in alcohol, ether, and chloroform but soluble in mixture of methylene chloride and methanol. It is very stable in dry condition from pH 3.0 to 11.0. Aqueous solutions are liable to be affected by microorganism (Handbook Pharmaceutical Excipients, 2005).[24]

MATERIALS AND EQUIPMENTS [TABLES 3 AND 4]

Dose Calculation

The amount of drug required in a controlled release dosage form, to provide a sustained drug level in the body is determined by the pharmacokinetics of the drug, the desired therapeutic level of the drug, and the intended duration of action. The objective of this calculation is to arrive at the theoretical amount of drug that must be present in the FDDS, being administered once a day and capable of acting up to 12 h. In general, the total dose required (DTotal) is the sum of the maintenance dose (DM) and the initial dose (DI) immediately released to provide a therapeutic blood level.
DTotal = DI + DM

Table 3: Materials used in the work

S. No.	Materials	Vendor
1	Lamivudine	A generous gift from Dr. REDDY'S Laboratories, Hyderabad
2	Gelucire 43/01	A generous gift from GATTEFOSSE Corp, France
3	HPMC K100M	A generous gift from ISP Hongkong Pvt. Ltd., Hyderabad.
4	HPMC K4M	A generous gift from ISP Hongkong Pvt. Ltd., Hyderabad
5	Compritol 888 ATO	A generous gift from Shasun Pharmaceuticals Pvt. Ltd., Pondicherry
6	Precirol ATO 5	A generous gift from Shasun Pharmaceuticals Pvt. Ltd., Pondicherry
7	Lubritab	A generous gift from Aurobindo Pharma Pvt. Ltd., Hyderabad
8	Cremophor	A generous gift from Aurobindo Pharma Pvt. Ltd., Hyderabad

Table 4: Equipment used in the work

S. No.	Equipment	Manufacturer	Model No
1	Electronic Single Pan Balance	Shimadzu	GP3202
2	Dissolution apparatus	Lab India	Disso 2000
3	UV spectrophotometer	Cyberlab	3220 UV
4	IR spectrophotometer	Nicolet	5700
5	DSC	Breeze	DSCQ1000
6	Heating mantle	Biotechniques, India	BTIL
7	Hot pan	Remi Equipment	1MLH
8	Flask shaker	Kemi	KRS2
9	Hot air oven	Dolphin	75177
10	Mesh #16,40	Jayant	ASL00

In practice, DM (mg) is released over a period of time and is equal to the product of td (duration of action per hour) and the zero-order rate k°r (mg/hr). Therefore, the equation can expressed as

DTotal = DI + kotd

Ideally, the maintenance dose (DM) is released after DI has produced a blood level equal to the therapeutic drug level. However, due to the limits of formulations, DM actually starts to release at t = 0. Therefore, DTotal may be reduced from the calculated amount to avoid " tapping"

DTotal = DI – Kot + Kotd

The equation describes the total dose of the drug needed, with "t" representing the time needed to reach peak drug concentration after the initial dose.

Pharmacokinetic Parameters of Lamivudine

Elimination half-life (t1/2) = 1.6 h

Time to reach peak plasma concentration (TMax) = 1 h Conventional dose = 30 mg.

Calculations involved in the preparation of lamivudine controlled release formulations

Conventional dose of lamivudine was found to be 20 mg. This was considered as initial dose (DI).

Calculation for elimination rate constant (KE)

KE = 0.693/t1/2

= 0.693/1.6

= 0.433/h

Calculation of zero-order release rate constant (Ko)

Desired release rate from maintenance dose

KO = DI × KE

= 30 × 0.433

= 12.9 mg/h.

Calculation of maintenance dose (DM)

DM = Ko [T – t1/2]

= 12.9 × (12-1.6)

= 12.9 × 10.4

= 134.16 mg

Calculation involved in correcting the initial loading dose (DI)*

DI* = DI - [Ko × TMax]

= 30-[12.9 × 1] = 17.1 mg

Calculation of total dose

Total dose = DM + DI*

= 17.1 + 134.16 = 151.26 mg

The dose was rounded off to 150 mg for convenience.

Construction of Theoretical Release Profile of Lamivudine

Theoretical release profile of a drug is constructed to check whether the formulations are releasing the drug similar to the predicted profile. In case of lamivudine, a loading dose of 30 mg may be sufficient. To attain therapeutic level, drug input rate of 12.9 mg/hr is required for maintenance of therapeutic concentration of the drug.

A dose of 43 mg must be released with TMax, that is, 1.6 h which was taken as 2 h. Subsequently, an hourly dose of 10.7 mg should be released, finally at the 12th h, the total drug should be released [Table 5].

Finally at the 12th h, the total drug should be released [Table 5] for 150 mg of lamivudine.

RESULTS AND DISCUSSION

In the present study, lamivudine was selected as model drug in the design as GFDDS using various lipoidal/fatty polymers. Lamivudine complies with all the requirements that are suitable for a drug candidate to be formulated as GFDDS, as it has

Table 5: Theoretical amount released and percent released values of lamivudine

Time (h)	Amount of lamivudine released (mg)	Percent released
0	0	0
2	43	28.38
4	64.4	42.50
6	85.8	56.62
8	107.2	70.75
10	128.2	84.61
12	150	100

specific site of absorption in upper part of GIT. Since the half-life of lamivudine is 1.6 h, multiple doses are needed to maintain plasma concentration for a good therapeutic response and improved patient compliance.

A 150 mg dose of lamivudine was obtained from sustained release calculations to maintain its effective plasma drug concentrations for 12 h.

GFDDS of lamivudine was developed, to avoid fluctuations in the plasma drug concentrations as well as for increasing bioavailability of lamivudine. The GFDDS retains in the stomach and thereby improves the bioavailability of drugs that have an absorption window in a particular region of the GI tract than conventional oral controlled delivery systems.

CONCLUSION

Oral drug administration is by far the most preferable route for taking medications. However, the therapeutic window of many drugs is limited by their short circulating half-life and absorption through a defined segment of the GIT. Such pharmacokinetic limitations may lead in many cases to frequent dosing of these medications to achieve the required therapeutic effect and hence poor patient compliance.

Majority of drugs are having site specific absorption in the gastrointestinal tract and parameters such as pH-dependent solubility, stability, and ionization of the drug in different portions of the G.I. tract, influence such absorption. GRT is one of the important factors, which adversely affect the absorption of drugs when administered simply by an oral controlled delivery system.

Gastroretentive FDDS possesses the ability of being retained in the stomach and help in optimizing the oral controlled delivery of drugs having absorption window by continuously releasing drug for prolonged period of time thus ensuring optimal biological absorption (BA).

Many attempts have been made in recent years to provide a dosage form with longer GRT and therefore a more efficient absorption. FDDS is well proved and documented to be therapeutically superior to conventional dosage system in number of studies. Hence, the aim was "in accordance with the therapeutic objective, to design and evaluate hydrodynamically balanced non-effervescent FDDS of lamivudine as controlled release modules," which prolongs the release rate of the drug while extending the residence time of the drug within the body environment and without causing undeleterious effects to the subject. Lamivudine is a potential anti-HIV agent, used for the long-term treatment of HIV-1 infection. It is least absorbed from lower part of the GIT and it has higher absorption (specific site of absorption) in the proximal region of the GI tract, that is, stomach and it has short biological half-life (0.8–1.6 h) following oral administration. All of these factors favor the drug candidature feasible to formulate as a gastroretentive system.

The present work was carried with an in house experimental design to prepare multiunit granule GFDDS employing successful cellulose polymers and various efficient lipoidal/fatty polymers with a motto to optimize best polymer among all of them for formulation of hydrodynamically balanced FDDS of lamivudine.

Lamivudine multiunit granule GFDDS with controlled matrix cellulose and lipoidal polymers was prepared by different granulation techniques in the ratio of 1:1, 1:1.5, and 1:2.

Lamivudine multiunit formulations comprising cellulose polymers were prepared by wet granulation technique, whereas the lamivudine multiunit formulations comprising lipoidal/fatty polymers were prepared by melt granulation technique.

All the multiunit granule formulations (F1–F21) prepared were evaluated for drug content and all the formulations had shown good results within the official limits. They are even assessed for flow characteristics such as bulk density, tapped density, Carr's index, and Hausner ratio. Formulations with cellulose polymers had shown excellent flow characters whereas formulations prepared employing lipoidal polymers had shown a bit inferior results to cellulose polymers as they are prepared by melt granulation, but are passable.

The entire prepared multiunit granule GFFDS was subjected to *in vitro* buoyancy studies that are

carried out in 0.1 N HCl. All the formulations F1–F21 were tested for floating parameters like floating lag time and floating duration time. Formulations prepared with cellulose polymers in different drug to polymer proportions (F1, F2, F8, F9, F15, and F16) had shown buoyancy lag time which might be the time taken for hydrogel formation, whereas all the other formulations prepared with lipoidal polymers in different drug to polymer proportions had floated from 0 time. However, in case of multiunit formulations prepared with Compritol 888 ATO and Precirol ATO 5, 10–20% and 60% of granules, respectively, had shrinked to the bottom after 2 h. Other multiunit GFDDS prepared with Lubritab, Cremophor, and Gelucire 43/01 had shown excellent buoyancy characteristics beyond 12 h of study.

The *in vitro* drug release studies of the entire prepared multiunit GFDDS were studied separately according to their proportions (1:1, 1:1.5, and 1:2) using 0.1 N HCl as medium in USP XXIV paddle-type dissolution apparatus.

Assessment of dissolution study results revealed that formulations F7 (Lamivudine: Gelucire 43/01 – 1:1), F10 (Lamivudine: Compritol 888 ATO – 1:1.5), and F19 (Lamivudine: Lubritab – 1:2) had retarded the drug release in controlled manner up to 12 h. Hence, these formulations were considered as promising formulations. Even though formulation F10 employing Compritol 888 ATO had retarded the drug release up to 12 h, due to its poor buoyancy characteristics, some extent of granules had shrinked, which is not desirable for a GFDDS. Formulation F19 prepared with Lubritab as controlled floating polymer had retarded the drug release up to 12 h successfully, but at a high drug to polymer concentration of 1:2.

Formulation F7 prepared with low concentration of Gelucire (1:1 proportion) had retarded the release of lamivudine in a rate controlled manner up to desired 12 h. Since the formulation F7 utilized less polymer concentration, it was considered as the best optimized formulation among other formulations.

The optimized formulation F7 was evaluated for its floating ability and *in vitro* drug release studies against single unit GFDDS prepared employing same polymer, that is, Gelucire 43/01 with drug-to-polymer ratio of 1:3. By comparing the buoyant characteristics and release characteristics among F7 and single unit, single unit GFDDS had shown excellent floating ability for more than 12 h, also the drug release was found to be 81% for 12 h, by an unknown mechanism of drug release.

The dissolution characteristics of optimized multiunit formulation F7 are compared with that of the pure drug and marketed formulation (STAVIR). Pure drug had shown its high hydrophilic characteristics by releasing 93% of drug in 0.5 h itself, where as lamivudine marketed formulation STAVIR had shown drug release of more than 97% in 1 h.

To establish the mechanism of drug release, the experimental data were fitted to five popular exponential equations. The drug release of lamivudine prepared from cellulose polymers (by wet granulation) and from the lipoidal/fatty polymers (by melt granulation) followed zero-order kinetics which was clearly indicated by higher "r" values of zero-order release when compared to those of first-order release model.

The relative contributions of drug diffusion and matrix erosion to drug release were further confirmed by subjecting the dissolution data to Higuchi model and erosion model. It was found that all the formulations followed diffusion mechanism as indicated by their higher "r" values.

By fitting all the data into Korsemeyer–Peppas model (Power Law), all the formulations had shown exponent "n" values above 1 indicating the drug release strictly followed zero-order super case II transport as the drug release mechanism.

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