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PREPARATION AND EVALUATION OF CONTROLLED RELEASE MATRIX TABLETS OF LAMIVUDINE

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Abstract:

The present investigation is aimed at formulating and evaluating controlled release matrix tablets of Lamivudine using different polymers such as HPMC, Ethylcellulose, EudragitRL-100 due to their biocompatibility and cost effectiveness.Lamivudine is a potent hydrophilic anti viral agent indicated for treatment of AIDS. It belongs to class III of the BCS Classification with High solubility and low permeability. The polymers were taken at 20%,and 40% of the total weight of the tablet which is kept at a weight of 500 mg with a oral dose of 300 mg of the drug.The physical mixture was evaluated prior to compression for determining the flow properties. These tablets were evaluated for weight variation, hardness, thickness, friability, content uniformity and in-vitro drug release profile. It was found that the cumulative percent drug release decreased with increasing concentration of polymers. All the formulations were able to retard the release of the drug beyond 12 hours.F4 (20% HPMC) formulation was selected as optimized formulation.The swelling study shows that the swelling index was increased up to 6 hours and there after that the swelling index was decreased. No chemical interaction between Drug and the Polymers were seen as confirmed by FT-IR studies. Thus, sustained release matrix tablets of Lamivudine using biocompatible polymers were successfully formulated, evaluated and found to be suitable candidates in extending the release of the drug from the matrix tablets.

Keywords: *Lamivudine,HPMC,EthylCellulose,EudragitRL-100,Matrix Tablets.*

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INTRODUCTION:

In the recent years considerable attention has been focused on the development of new drug delivery systems. Pharmaceutical research since 1950 turned to a new era towards optimizing the efficacy of the drug by designing the drug in different dosage forms posing challenges to the pharmaceutical technologists. For many decades treatment of acute diseases or chronic illness have been mostly accomplished by delivery of drugs to patients using various pharmaceutical dosage forms, including tablets, capsules, suppositories, creams, ointments, liquids, aerosols, and injectables. The oral conventional types of drug delivery systems are known to provide a prompt release of drug [1-6].

Therefore, to achieve as well as to maintain the drug concentration within the therapeutically effective range needed for treatment, it is often necessary to take this type of drug delivery systems several times a day. This results in a significant fluctuation in drug levels often with sub-therapeutic and/or toxic levels and wastage of drug. In recent years, various modified-release drug products have been developed to control the release rate of the drug and/or the time for drug release [7-9].

The term modified-release product is used to describe products that alter the timing and/or the rate of release of the drug substance. A modified-release dosage form is defined "as one for which the drug-release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional and immediate-release dosage forms such as solutions, ointments, or promptly dissolving dosage forms as presently recognized".

An ideal drug delivery system involves two pre requisites. It should deliver the drug at a rate desired by the needs of the body, over the period of the treatment. This necessitates steady state blood levels or a tissue level that is therapeutically effective and non toxic for an extended period of time. It should channel the active entity to the site of action. Advanced research in pharmaceutical technology would find several controlled release dosage forms in the market. These products have been identified by various names as “sustained release”, “prolonged release”, “controlled release”, “timed release”, and “delayed release”.

Conventional Drug Delivery System [10-13]

Pharmaceutical products designed for oral delivery are mainly conventional drug delivery systems, which are designed for immediate release of drug for rapid/immediate absorption.

As can be seen in the graph (Figure 1), administration of the conventional dosage form by extra vascular route does not maintain the drug level in blood for an extended period of time. The short duration of action is due to the inability of conventional dosage form to control temporal delivery.

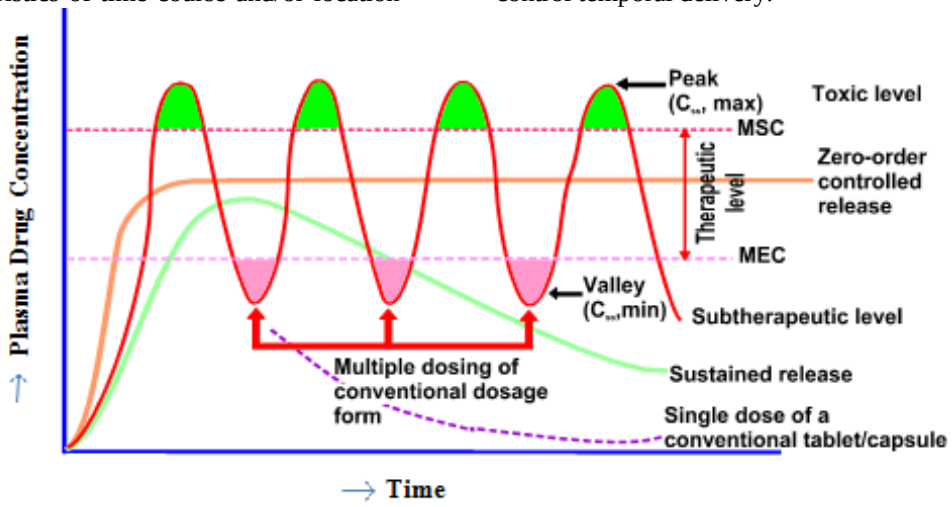

Fig 1: A hypothetical plasma concentration-time profile from conventional multiple dosing and single doses of sustained and controlled delivery formulations. (MSC = maximum safe concentration, MEC = minimum effective concentration).

The conventional dosage forms like solution; suspension, capsule, tablets and suppository etc. have some limitations such as

1) Drugs with short half-life require frequent administration, which increases chances of missing the dose of drug leading to poor patient compliance.
2) A typical peak-valley plasma concentration-time profile is obtained which makes attainment of steady state condition difficult. The unavoidable fluctuations in the drug concentration may lead under medication or overmedication as the steady state concentration values fall or rise beyond the therapeutic range.

The fluctuating drug levels may lead to precipitation of adverse effects especially of a drug with small therapeutic index, whenever overdosing occurs.

In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of controlled drug delivery system that could revolutionize method of medication and provide a number of therapeutic benefits.

Controlled Release Drug Delivery Systems (CRDDS) [14,15]

More precisely, controlled delivery can be defined as,

1) Sustained drug action at a predetermined rate by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects.
2) Localized drug action by spatial placement of a controlled release system adjacent to or in the diseased tissue.
3) Targeted drug action by using carriers or chemical derivatives to deliver drug to a particular target cell type.
4) Provide a physiologically / therapeutically based drug release system. In other words, the amount and the rate of drug release are determined by the physiological/ therapeutic needs of the body.

Advantages of Controlled Drug Delivery System

1. Overcome patient compliance problems.
2. Employ less total drug
   a) Minimize or eliminate local side effects
   b) Minimize or eliminate systemic side effects
   c) Obtain less potentiation or reduction in drug activity with chronic use.
   d) Minimize drug accumulation with chronic dosing.
3. Improve efficiency in treatment
   a) Cures or controls condition more promptly.
   b) Improves control of condition i.e., reduced fluctuation in drug level.
   c) Improves bioavailability of some drugs.
   d) Make use of special effects, e.g. Sustained-release aspirin for morning relief of arthritis by dosing before bed time.
4. Economy i.e. reduction in health care costs. The average cost of treatment over an extended time period may be less, with lesser frequency of dosing, enhanced therapeutic benefits and reduced side effects. The time required for health care personnel to dispense and administer the drug and monitor patient is also reduced.

Disadvantages:

1) Decreased systemic availability in comparison to immediate release conventional dosage forms, which may be due to incomplete release, increased first-pass metabolism, increased instability, insufficient residence time for complete release, site specific absorption, pH dependent stability etc.
2) Poor in vitro – in vivo correlation.
3) Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitivity reactions.
4) Reduced potential for dose adjustment of drugs normally administered in varying strengths.

Mechanism of Drug Release from Matrix Tablets

In erodible matrices, polymer erosion from the surface of the matrix determines the drug release; whilst in hydrophilic matrices, formation of the gel layer and its dynamics as a function of time determines the drug release. Gel layer thickness, which determines the diffusion path length of the drug, corresponds to the distance between the diffusion and erosion fronts. As the swelling process proceeds, the gel layer gradually becomes thicker, resulting in progressively slower drug-release rates; however, due to continuous hydration, polymer disentanglement occurs from the surface of the matrix, resulting in a gradually decreasing depletion zone and an increased dissolution

METHODOLOGY:

Formulation

Table 1: Composition of Matrix Tablets Containing HPMC, Ethyl cellulose, Eudragit RL-100

Total tablet weight to polymer concentration is 30%, 40%, and 50%

Formulation Code	Drug (mg)	HPMC	Ethyl cellulose	Eudragit RL-100	Avicel PH 101	Magnesium sterate	Talc	Aerosil	Tablet Wt.
F1	300	130	-	-	50	10	10	-	500
F2	300	100	-	-	80	10	10	-	500
F3	300	80	-	-	100	10	10	-	500
F4	300	60	-	-	120	10	10	-	500
F5	300	-	120	-	63	3	9	5	500
F6	300	-	160	-	26	3	6	5	500
F7	300	-	-	120	63	3	9	5	500
F8	300	-	-	160	26	3	6	5	500

Total tablet weight to polymer concentration is 20% and 40%.

Evaluation of Pre-compression Blend

a) Angle of Repose:

The angle of repose of granules was determined by the fixed funnel-method. Angle of repose was calculated using the following equation.

$$\mathbf{Tan\theta = h/r}$$

Where h and r are the height and radius of the powder cone, θ is the angle of repose.

b) Determination of Bulk Density and Tapped Density:

The bulk density and the tapped density were calculated using the following formulae.

Bulk density = W/V_0, Tapped density=w/vf

Where, W= Weight of the powder, V_0 = Initial volume, V_f = final volume

c) Compressibility Index (Carr's Index):

Carr's index (CI) is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is

CI = (TD-BD) x 10

Where,

TD is the tapped density and BD is the bulk density.

d) Hausner's Ratio:

It is the ratio of tapped density and bulk density. Hausner found that this ratio was related to interparticle friction and, as such, could be used to predict powder flow properties.Generally a value less than 1.25 indicates good flow properties, which is equivalent to 20% of Carr's index. And greater than 1.5 indicates that poor flow, in between these values passable.

Evaluation of Matrix Tablets:

Thickness: Twenty tablets from the representative sample were randomly taken and individual tablet thickness was measured by using digital vernier caliper. Average thickness and standard deviation values were calculated.

Hardness:

Tablet hardness was measured by using Monsanto hardness tester. From each batch six tablets were measured for the hardness and average of six values was noted along with standard deviations.

Friability Test:

% friability was calculated as follows

$$\% \text{ Friability} = (W_1 - W_2) \times 100/W_1,$$

Where W_1 = Initial weight of the 10 tablets.

W_2 = Final weight of the 10 tablets after testing.

Weight Variation Test:

To study weight variation individual weights (W_I) of 20 tablets from each formulation were noted using electronic balance. Their average weight (W_A) was calculated. Percent weight variation was calculated as follows. Average weights of the tablets along with standard deviation values were calculated.

$$\% \text{ weight variation} = (W_A - W_I) \times 100/ W_A$$

Drug Content Uniformity (Assay):

The drug content of the matrix tablets was determined according to in-house standards and it meets the requirements if the amount of the active ingredient in each of the 10 tested tablets lies within the range of 90% to 110% of the standard amount.

***In -Vitro* Drug Release Characteristics:**

Drug release was assessed by dissolution test under the following conditions: n = 3, USP type I dissolution apparatus (Basket method).

RESULTS AND DISCUSSION:

Table 2: Standard Graph of Lamivudine

Concentration (µg/ml)	Absorbance(nm)
0	0
5	0.14
10	0.25
15	0.34
20	0.44
25	0.52
30	0.63
35	0.72
40	0.85
45	0.92
50	0.99
R^2	0.996

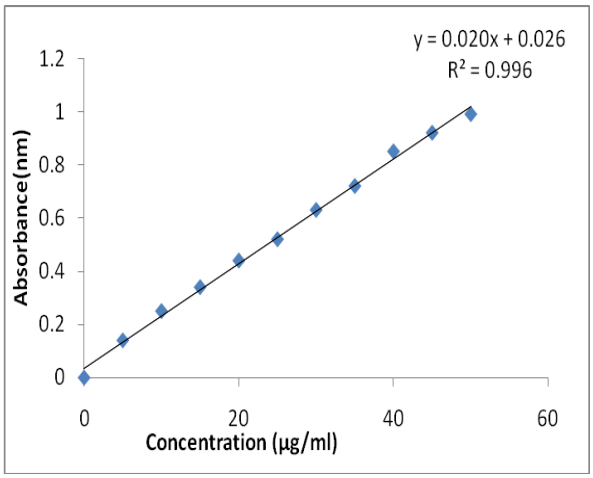

Fig 2: Standard graph of Lamivudine in 6.8 pH buffer.

Table 3: Precompression Evaluation of Lamivudine Formulations:

Formulation code	Angle of repose(θ)	Bulk density (g/ml)	Tapped density (g/ml)	Hausner's ratio	Carr's index (%)
F1	22.54±0.99	0.33±0.98	0.38±0.57	1.15	13.15
F2	21.45±0.61	0.30±0.13	0.35±0.69	1.16	14.28
F3	21.57±0.91	0.35±0.32	0.41±0.27	1.17	14.63
F4	21.26±0.46	0.33±0.57	0.39±0.09	1.18	15.38
F5	22.26±0.14	0.31±0.29	0.35±0.18	1.14	11.42
F6	23.23±0.84	0.35±0.67	0.41±0.89	1.16	14.63
F7	21.78±1.27	0.35±0.28	0.41±1.51	1.18	14.69
F8	20.74±0.22	0.33±0.32	0.41±0.96	1.24	19.51

Table 4: Post Compression Evaluation Studies for Lamivudine Matrix Tablets:

Formulation code	Hardness ±SD †	Wt variation ±SD ‡	Friability	Thickness ±SD ‡	Assay ± SD *
F1	4.3±0.57	497.5±1.42	0.62	4.52±0.13	98.23±0.67
F2	4.0±0.15	499.0±0.71	0.75	4.31±0.15	97.52±1.25
F3	4.5±0.27	500.0±2.01	0.66	4.09±1.14	98.41±0.71
F4	5.0±0.32	498.3±1.43	0.87	4.27±0.82	99.71±0.63
F5	4.6±0.55	496.5±0.98	0.98	4.65±0.00	96.67±0.77
F6	4.2±1.51	499.0±2.70	0.92	4.15±0.02	98.12±0.46
F7	4.0±0.76	500.5±0.70	0.86	4.42±0.72	96.41±1.15
F8	4.8±0.44	497.2±0.35	0.71	4.60±0.05	98.25±0.75

** All values represent mean ± Standard Deviation (SD), n=3*
† All values represent mean ± Standard Deviation (SD), n=6
‡ All values represent mean ± Standard Deviation (SD), n=20

***In-vitro* Drug Release Studies:**

Drug Release from HPMC:

The results of release studies of formulations F1-F4 are shown in Table 15 & 16 and Figure 6 & 7. The release of drug depends not only on the nature of matrix but also upon the drug polymer ratio. As the percentage of polymer increased, the kinetics of release decreased.

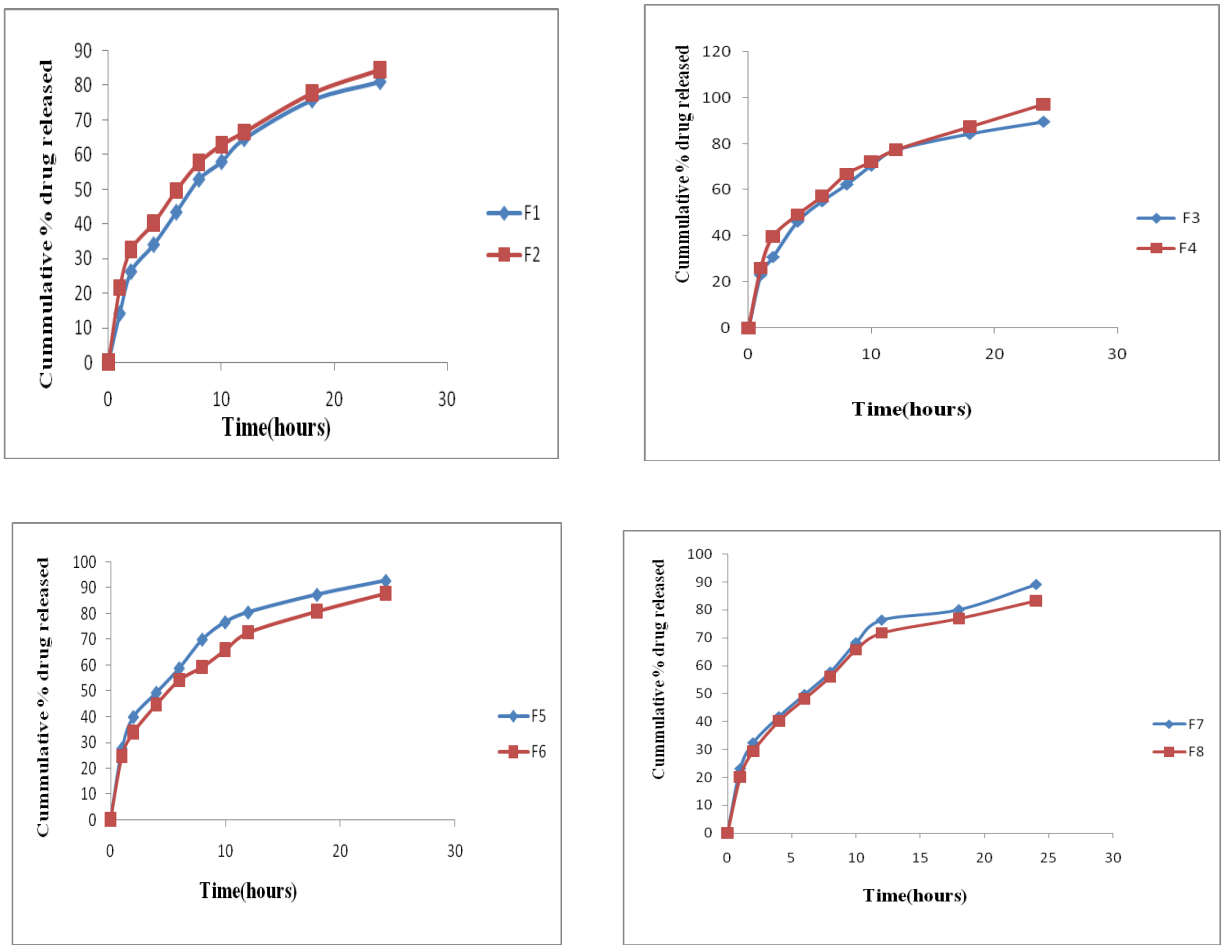

Fig 3: Release Rate Profiles of Lamivudine from HPMC (F1-F4), Ethyl cellulose (F5, F6), Eudragit RL-100(F7,F8).

FT-IR Studies:

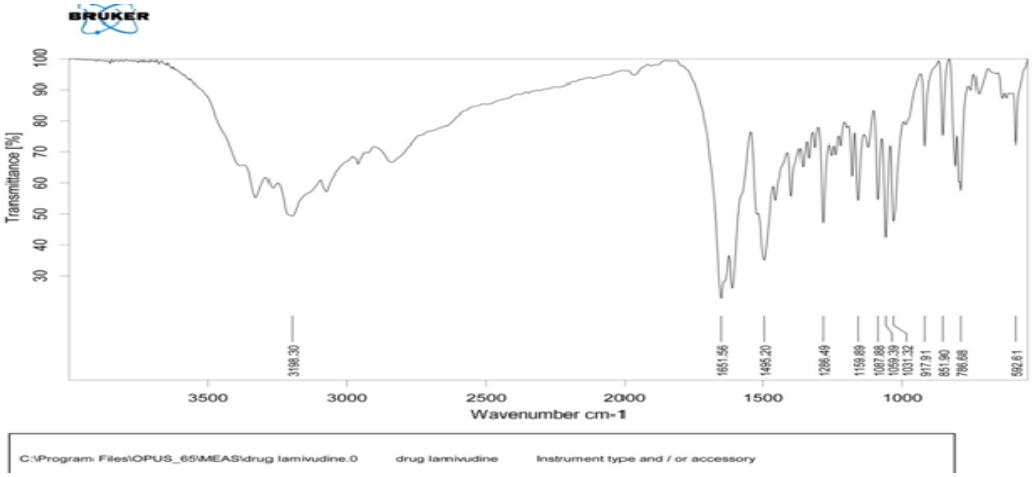

Fig 4: FTIR Spectrum of Lamivudine

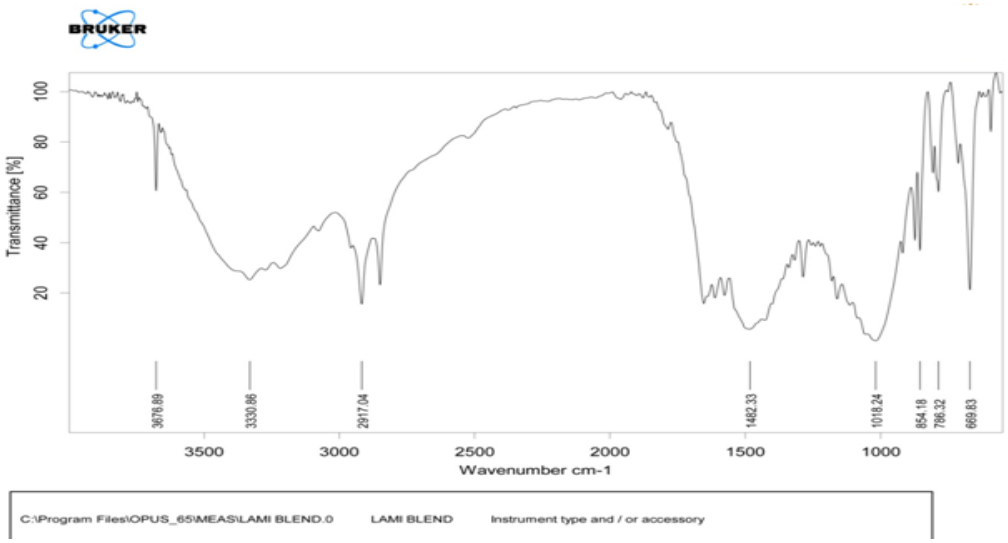

Fig 5: FTIR Spectrum of Optimized Formulation

Table 5: Drug Release Kinetics of Optimized (F4) Matrix Tablets

Zero order		First order		Higuchi		Hixson-Crowell		Korsmeyer-Peppas		
r^2	K_0 (h^{-1})	r^2	K_1 (h^{-1})	r^2	K_H ($h^{-1/2}$)	r^2	K_{HC} ($h^{-1/3}$)	r^2	n	K_{KP} (h^{-n})
0.815	3.434	0.370	0.046	0.978	19.53	0.885	9.491	0.553	0.38	0.882

r^2 = Correlation coefficient; K = Kinetic constant; n= Diffusional exponent.

Table 6: Swelling Study of Optimized Formulation (F4):

Time (hours)	% Swelling
2	125.22
4	226.36
6	228.55
8	175.08
10	154.21
12	123.84

CONCLUSION:

Optimized formulation F4 (drug to polymer ratio 1:0.23) which includes 20% HPMC has successfully sustained the drug release for 10-12 hours and the drug release pattern was similar to theoretical release profile. The release process involves anomalous diffusion mechanism or diffusion coupled with erosion, as indicated by the n value of 0.38 in Korsmeyer's plot. There was an alteration in the surface area and diameter of the tablets with the progressive dissolution of the matrix as a function of time, as indicated in Hixson-Crowell plot. FTIR studies proved the no chemical interaction in drug and polymer of the developed matrix tablets.

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