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Formulation and evaluation of lamivudine controlled release tablets

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ABSTRACT

The Controlled released tablets containing Lamivudine were successfully prepared by direct compression by using Xanthum, Guar gum, HPMC, and CMC. The physiochemical evaluation results for the granules of all trials pass the official limits in angle of repose, compressibility index .The prepared granules were also maintained the physiochemical properties of tablets such as thickness, hardness, weight variation, friability and uniformity of drug content. The optimized formulation contains the average thickness of 2.43±0.25, average hardness of 7.3±0.57, average weight of 399 ± 1.11, friability of 0.08±0.57and drug content 98.22±0.57% .Based on various evaluation parameters formulations F5 was selected as optimized formulation and were further subjected for comparative *in vitro* drug release studies but among this F5 was optmised based highest percentage of drug release. Results revealed that all the formulated tablets had acceptable physical properties and showed release up to 97% in 24 Hrs. The optimized formulation was subjected for Zero order, First order, Higuchi matrix, and then Peppas model. The kinetic studies revealed that the formulation follows zero order indicates that rate of drug release is independent upon concentration.

Keywords: XANTHUM, GUAR GUM, HPMC, and CMC

INTRODUCTION

Oral solid dosage forms

A solid dosage form is drug delivery system that includes tablets, capsules, sachets and pills as well as a bulk or unit-dose powders and granules. Among the various dosage forms oral solid dosage forms have greater importance and occupy a prime role in the pharmaceutical market. Oral route of drug administration is widely acceptable and drugs administered orally as solid dosage form represents the preferred class of products. Over 90% of drugs formulated to produce systemic effects are produced as solid dosage forms. Because of these reason whenever New chemical entity (NCE) has discovered, which shows a sufficient pharmacological action, first the pharmaceutical company asks whether the drug is successfully administered by oral route or not. The oral route of administration still continues to be the most preferred route due to its manifold advantages including:

- Tablets and capsules represent unit dosage forms in which the accurate dose of drug to show sufficient pharmacological action can be administered. In case of liquid oral dosage

forms such as Syrups, Suspensions, Emulsions, Solutions and Elixirs the patient is asked to administer the medication of 5-30 ml. Such dosage measurements are typically error by factor ranging from 20-50 %, when the drug is self-administered by patient.

- Solid dosage forms are less expensive to shipping and less prone for the degradation when compared to liquid dosage forms[9].

Controlled-Release (CR) Preparations

The currently employed CR technologies for oral drug delivery are diffusion-controlled systems; solvent activated systems, and chemically controlled systems. Diffusion-controlled systems include monolithic and reservoir devices in which diffusion of the drug is the rate-limiting step, respectively, through a polymer matrix or a polymeric membrane. Solvent-activated systems may be either osmotically controlled or controlled by polymer swelling.

Chemically controlled systems release drugs via polymeric degradation (surface or bulk matrix erosion) or cleavage of drug from a polymer chain. It is worth mentioning here that the so-called programmed-release (‘‘tailored-release’’) profile of a final CR product is rarely the outcome of a single pharmaceutical principle. Depending on the specific physicochemical properties of the drug in question and desired therapeutic objectives, different formulation and CR principles may be proportionally combined within the same dosage form. This task appears to be simpler when realized in terms of appropriate selection of polymers and excipients that incorporate desired principles.

Controlled Release Drug Delivery Systems (CRDDS)

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[7].

A controlled drug delivery system is usually designed to deliver the drug at particular rate. Safe and effective blood levels are maintained for a period as long as the system continues to deliver the drug. This predetermined rate of drug release is based on the desired therapeutic concentration and the drug’s pharmacokinetics.

AIM AND OBJECTIVES OF THE STUDY

The main aim of the present work is to formulate and evaluate Lamivudine controlled release tablets. The fabrication of controlled release matrix tablet is by incorporating the drug in a matrix of rate controlling polymer(s) such as XANTHUM, GUAR GUM, HPMC, and CMC[11]. Primary objective of the work is to improves bio availability,to reduce dosing frequency through control released systems of lamivudine matrix tablets.

Individual objectives to be attained are: -

1. Preformulation studies on the drug.
2. Screening & Selection of suitable polymers.
3. Preparation of matrix using drug and polymer in different ratios
4. Study of Pre-Compression parameters.
5. Compression of matrix tablets.
6. Study of post compression parameters like hardness, weight variation, drug content and in vitro dissolution studies.

METHODOLOGY

Development of calibration curve for lamivudine

Determination of Standard Curve In 6.8ph phosphate buffer

a. Stock solution of 1000µg/ml of Lamivudine was prepared by dissolving 100mg of drug in 6.8 pH buffer and make up to 100ml volume
b. From this take 10ml and make up to 100ml using buffer to get a stock solution of 100 µg/ml.
c. From the above solution take 0.2, 0.4,

0.6 0.8, 1.0 1.2, 1.4 1.6ml and dilute to 10 ml with buffer to get a concentrations of 2,4, 6,8,10, and 12µg/ml.

d. The absorbance of the different diluted solutions was measured in a UV spectrophotometer at 270nm.

A calibration curve was plotted by taking concentration of the solution in µg/ml on X-axis and absorbance on Y-axis and correlation co-efficient "r^2" was calculated.

Preparation of Standard Curve for Lamivudine

Determination of Standard Curve in 0.1 N HCl

a. Stock solution of 1000µg/ml of Lamivudine was prepared by dissolving 100mg of drug in 0.1 N Hcl buffer and make up to 100ml volume

b. From this take 10ml and make up to 100ml using buffer to get a stock solution of 100 µg/ml.

c. **c)** From the above solution take 0.2, 0.4, 0.6 0.8,1.0 1.2,1.4 1.6,ml and dilute to 10 ml with buffer to get a concentrations of 2,4, 6,8,10, and 12µg/ml.

d. The absorbance of the different diluted solutions was measured in a UV spectrophotometer at 270nm.

A calibration curve was plotted by taking concentration of the solution in µg/ml on X-axis and absorbance on Y-axis and correlation co-efficient "r^2" was calculated..

Preparation of Lamivudine Matrix Tablets

All the matrix tablets, each containing 150 mg of lamivudine, formulations were prepared by direct compression method also to study the effect of method of manufacture on the drug release.

Direct compression

Accurately weighed amounts of drug, polymer, and diluent were mixed geometrically in a mortar[10]. This mixture was passed through No.40 sieve and thoroughly mixed in a polythene bag for 15 minutes. The powder blend was then lubricated with magnesium stearate and for 2 minutes and compressed into tablets on a 8-station rotary tableting machine using 8mm round, flat-faced punches.

The drug polymer ratio was developed to adjust drug release as per theoretical release profile and to keep total weight of tablet constant for all the fabricated batches under experimental conditions of preparations[4]. The total weight of the matrix tablets was 400mg with different drug polymer ratios. The various polymers used were HPMC, Guargum, CMC, and xanthum. fillers like MCC (water soluble),lubricants like magnesium stearate were used for the preparation of matrix tablets.

Formulations

In the formulations prepared, the release retardants included were MCC were used as filler[3]. Magnesium stearate (MS) 1% were used as lubricants. Compositions of different formulations were given in the following Tables.

Table 1 . Composition of Matrix Tablets Containing

F.Code	F1	F2	F3	F4	F5	F6	F7	F8
API (mg)	150	150	150	150	150	150	150	150
Xanthum	100	-	-	-	100	100	-	-
Guar gum	-	100	-	-	-	-	100	100
HPMC K100M	-	-	100	-	100	-	100	-
CMC	-	-	-	100		100	-	100
Mg.stearate(mg)	4	4	4	4	4	4	4	4
MCC	146	146	146	146	46	46	46	46
Total (mg)	400	400	400	400	400	400	400	400

RESULTS AND DISCUSSION

Lamivudine standard curve in 6.8pH phosphate buffer

Table no2. standard Lamivudine curve values

S.no	Concentration	Absorbance
1	0	0
2	2	0.084
3	4	0.180
4	6	0.276
5	8	0.35
6	10	0.45
7	12	0.54

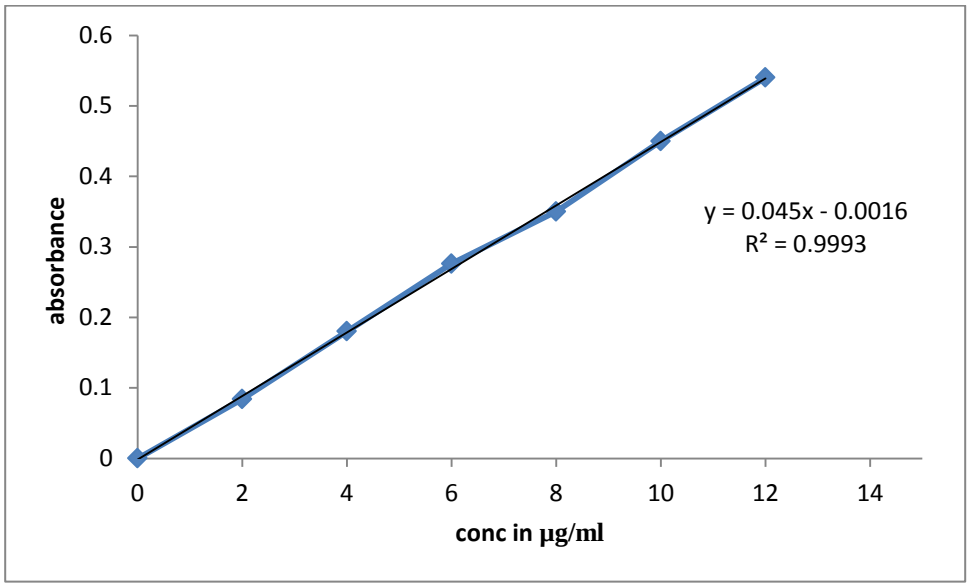

Fig.1 Lamivudine graph

Lamivudine standard curve in 0.1N Hcl

Table no 3. standard Lamivudine curve values

S.no	Concentration	Absorbance
1	0	0
2	2	0.096
3	4	0.191
4	6	0.283
5	8	0.375
6	10	0.475
7	12	0.576

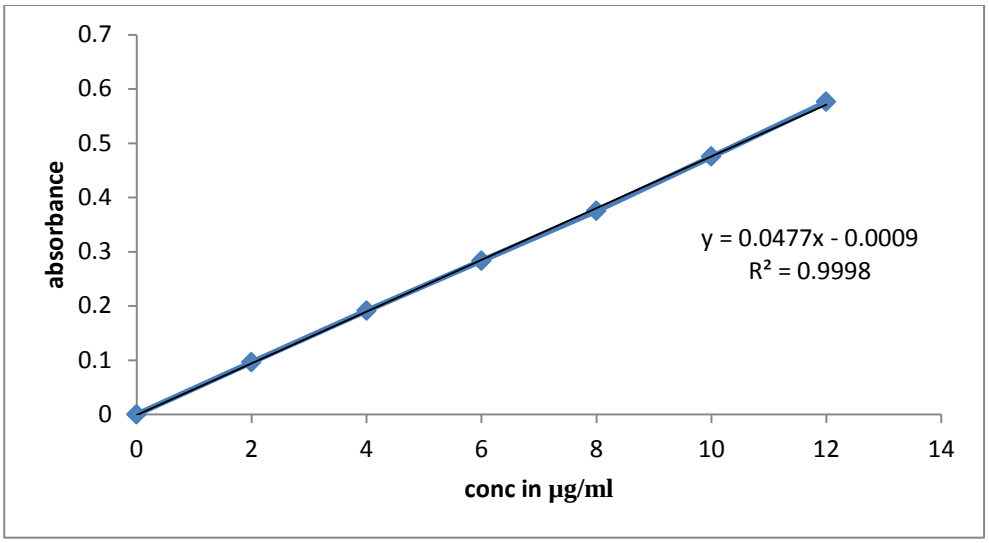

Fig.2 Lamivudine graph

COMPATABILITY STUDIES

The spectrum obtained after the analysis is shown in Figure No:3 The spectrum of the standard and the samples were then superimposed to find out any possible interactions between the drug and the polymers. All the characteristic peaks of Lamivudine mentioned in Table No:4 were also found in the spectrum formulations[5]. The results suggest that the drug is intact in the formulations and there is no interaction found between the drug and the excipients.

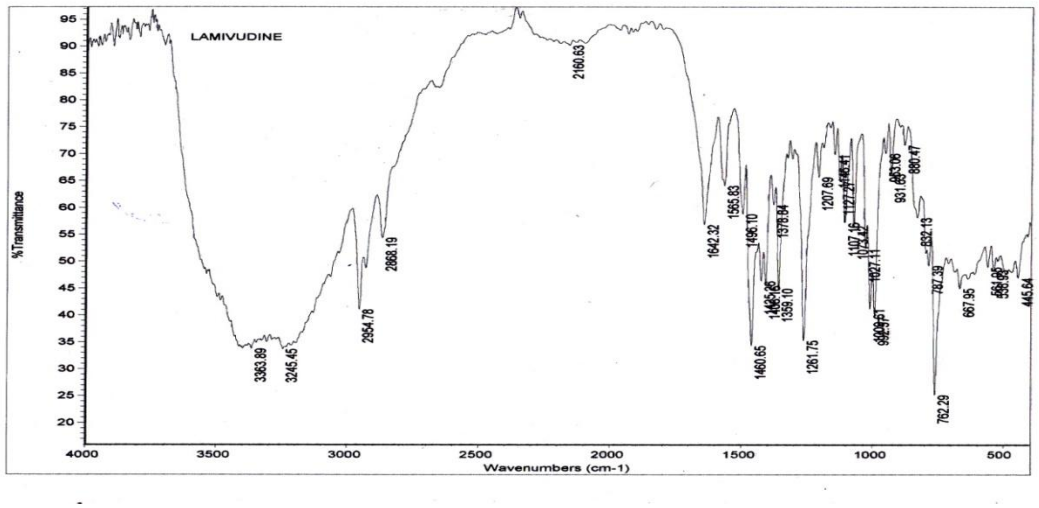

Fig:3 FTIR graph of Pure Lamivudine drug

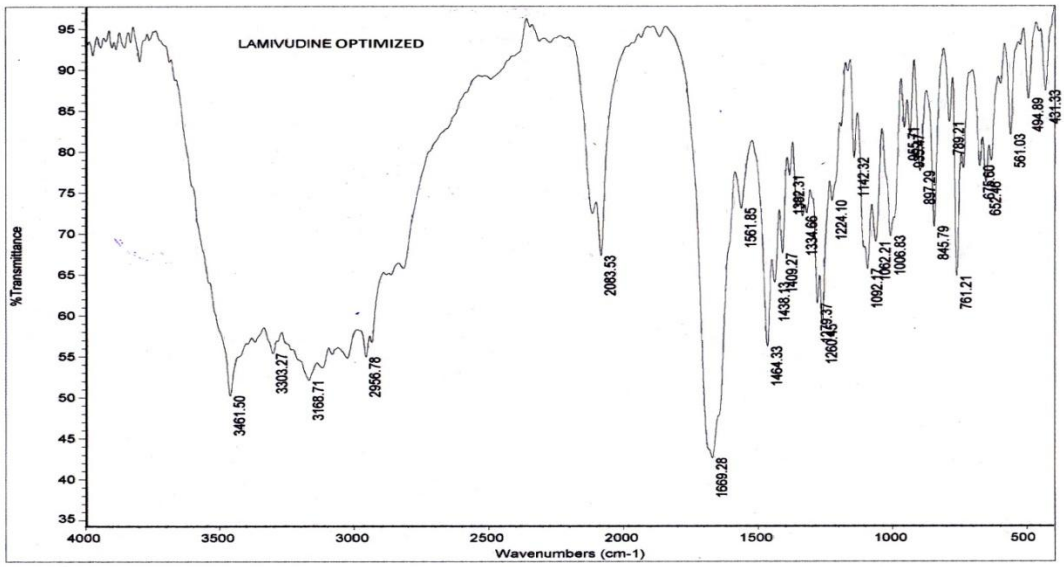

Fig: 4 FTIR graph of Lamivudine optimized formulation

Table no: 4 Interpretation data of lamivudine with optimized formulation

Functional groups	Lamivudine	Optimized formulation
	Observed peak	Observed peak
-NH2	3363.89	3461.50
-OH	3245.45	3303.27
-CH3	2954.73	2956.56
C=S	1107.16	1142.32

Melting point determination

The melting point of Lamivudine was found to be160.2°C, which complied with BP standards thus indicating purity of obtained drug sample.

PRE COMPRESSION PARAMAETRS

Table No: 5 pre compression parameters for Controlled Release Tablets

Formulations	Angle of Repose (θ)	Loose Bulk Density (g/ml)	Tapped Bulk Density (g/ml)	%Compressibility	Hausner's ratio	Angle of repose
F1	25^0 65'	0.321	0.354	9.322034	1.102804	Excellent
F2	25^0 73'	0.318	0.352	9.659091	1.106918	Excellent
F3	25^0 16'	0.315	0.342	7.894737	1.085714	Excellent
F4	26^0 68'	0.323	0.354	8.757062	1.095975	Excellent
F5	26^0 89'	0.321	0.358	10.3352	1.115265	Excellent
F6	27^0 58'	0.314	0.338	7.100592	1.076433	Excellent
F7	28^0 38'	0.312	0.335	6.865672	1.073718	Excellent
F8	26^0 42'	0.315	0.332	5.120482	1.053968	Excellent

From the above pre-compression parameters it was clear evidence that blends has excellent flow properties. All the formulations were evaluated for bulk density, tapped density, % compressibility, hausner's ratio and angle of repose. The results of % compressibility, hausner's ratio and angle of repose were found to be <10, <1.12 and <30 respectively. These results show that the formulations have excellent flow properties.

POST COMPRESSION PARAMETERS

Tablet No 6 -Post Compression Parameters for Controlled Release Tablets

SrNo	Hardness	Thickness	Friability	Drug content	Wt uniformity
F1	7.8±0.44	2.2±0.17	0.08±0.31	97.91±0.80	400 ± 1.1
F2	7.7±0.31	2.3±0.25	0.09±0.30	97.88±0.80	400 ±0.09
F3	7.2±0.40	2.3±0.80	0.05±0.57	99.88±0.57	399 ± 1.21
F4	7.2±0.55	2.4±0.20	0.07±0.40	96.82±0.66	400 ± 1.22
F5	7.3±0.57	2.43±0.25	0.08±0.57	98.22±0.57	399 ± 1.11
F6	7 .4±0.30	2.4±0.66	0.06±0.20	96.75±0.66	400 ± 0.08
F7	7.7±0.57	2.3±0.66	0.03±0.80	97.83±0.67	400 ± 0.07
F8	7.8±0.60	2.2±0.36	0.04±0.30	95.78±0.66	400 ± 0.03

The tablets were evaluated for weight variation, thickness, hardness, friability, drug content and *in-vitro* drug release study. All the formulations passed the evaluation tests and showed comparable satisfactory results[2].

The thickness of all tablets was found to be in the range of 2.2-2.43 mm and hardness was found to be in the range of 7.2-7.8kg/cm^2 in all the formulations. In all the formulations, the %friability was (0.03-0.09) below 1% as per USP.

The average weight was found to be 399-400mg which will be within the given limits. Hence all the tablets were found to show less weight variation. The drug content of all formulations ranged from 95% to 99%, which is within the specified IP limits.

INVITRO DISSOLUTION STUDIES FOR CONTROLLED TABLETS -

Dissolution study (controlled tablets)

Acidic Stage

Medium : 0.1N HCL
Type of apparatus : USP - II (paddle type)
RPM : 50
Volume : 900ml
Temperature : 37ºC± 0.5
Time : 2hrs

Buffer Stage

Medium : 6.8pH phosphate buffer
Type of apparatus : USP - II (paddle type)
RPM : 50
Volume : 900ml
Time : 22hrs

In vitro dissolution for controlled tablets were done initially in 0.1N HCL for 2hrs and next in 6.8 phosphate buffer for 24hrs.

Table no: 7In-Vitro Drug Release Studies for controlled release tablets

Time	F1	F2	F3	F4	F5	F6	F7	F8

	Dissolution medium 0.1N HCL							
1	3.4	6.7	4.3	16.3	2.3	8.6	3.6	10.8
2	14.8	16.5	12.6	33.8	8.8	15.2	20.8	29.6
	Dissolution medium pH6.8 buffer							
3	56.9	48.3	43.9	45.9	15.6	48.3	41.6	38.4
4	63.8	57.6	50.8	64.6	22.7	56.7	52.3	47.6
6	75.8	68.4	59.6	83.0	33.6	64.8	60.3	58.0
8	98.6	96.9	71.3	98.8	45.3	78.3	73.8	70.2
10	-	97.4	88.6	-	54.8	88.6	86.3	81.6
12	-	-	95.2	-	70.9	97.2	92.3	90.8
24		-	-	-	97.9	-	-	94.1

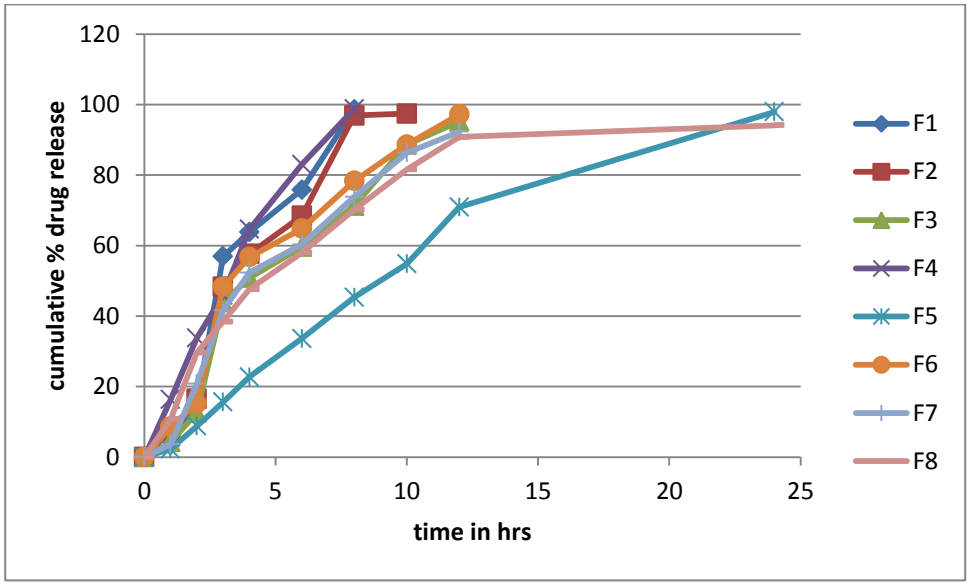

Fig 5: Dissolution profile graph for F1-F8

The results of release studies of formulations F1 to F8 are shown in table no 7. The release of drug depends not only on the nature of matrix but also upon the drug polymer ratio[1]. As the percentage of polymer increased, the kinetics of release decreased. Formulation F1, F2, F3,F4, ,F6, F7,F8 were failed to sustain release beyond 12h,.The formulation F5 was optimized because drug release was sustained up to 24hrs and followed USP guidelines[6].

RELEASE KINEITCS				
	ZERO	**HIGUCHI**	**PEPPAS**	**FIRST**
	Q Vs T	**Q Vs √T**	**Log C Vs Log T**	**Log % Remain Vs T**
Slope	**5.918**	**21.13**	**1.51**	**-0.04**
R 2	**0.9963**	**0.893**	**0.9417**	**0.95**

CONCLUSION

Based on various evaluation parameters formulations F5 was selected as optimized formulation and were further subjected for comparative *in vitro* drug release studies but

among this F5 was optmised based highest percentage of drug release.

Results revealed that all the formulated tablets had acceptable physical properties and showed release up to 97% in 24 Hrs[8]. The optimized formulation was subjected for Zero order, First order, Higuchi matrix, and then Peppas model. The kinetic studies revealed that the formulation follows zero order indicates that rate of drug release is independent upon concentration.

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