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**Development and Evaluation Sustained Release Matrices of Lamivudine by  
using Synthetic Polymer**

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**Abstract**

The present work is aimed at preparing and evaluating sustained release matrix tablets of Lamivudine using Synthetic polymer i.e. Glyceryl behenate (Compritol 888) with different polymers concentration by direct compression and Hot melt granulation techniques. Lamivudine is a potent hydrophilic anti viral agent indicated for treatment of AIDS (Acquired Immunodeficiency Syndrome). It was found that the cumulative percent drug release decreased with increasing concentration of Polymer. Matrix tablets were prepared by direct compression method and hot melt granulation technique taking Glyceryl behenate (Compritol 888) as different concentration in increasing order and F001 to F008 total eight formulation were prepared. The powders are evaluated for flow properties and tablets were evaluated for hardness, friability, dissolution rate, kinetics studies etc. No chemical interaction between Drug and the polymer were seen as confirmed by FT-IR studies. Among all the formulation made by direct compression and hot melt granulation it was found that the formulation containing Glyceryl behenate (Compritol 888) in higher concentration using Hot melt granulation showing best sustained release or retard the release of drug up to 24 hours.

**Keywords:** Lamivudine; Glyceryl behenate (Compritol 888); hot melt granulation; Sustained release.

**Contents**

1. Introduction . . . . .	508
2. Experimental . . . . .	509
3. Results and discussion . . . . .	511
4. Conclusion . . . . .	514
5. References . . . . .	514

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**1. Introduction**

Lamivudine is a potent hydrophilic anti viral agent indicated for treatment of AIDS (Acquired Immunodeficiency Syndrome). It belongs to class III of the BCS Classification with High solubility and low permeability. 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. The oral conventional types of drug delivery systems are known to provide a prompt release of drug [1-2]. 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. [3-7]. Lamivudine is a potent nucleoside analog reverse transcriptase inhibitor (nRTI) and it is the (-) enantiomer of a dideoxy analogue of cytidine. Lamivudine is rapidly absorbed with a bioavailability of over 80% following oral ingestion. The drug half-life in plasma is approximately 5-7 hours. It is bound to plasma proteins less than 36%. It can inhibit both types (1 and 2) of HIV reverse transcriptase and also the reverse transcriptase of hepatitis B [8]. The aim of present investigation was to design and evaluate sustained release matrix tablet with compritol 888 by direct compression and melt granulation technique and effect of polymer concentration on release kinetics of drug release, using distinct formulations.

## 2. Materials and Methods

### 2.1 Materials:

Lamivudine (LAM), Glyceryl behenate (Compritol 888), Lactose monohydrate, Aerosil, Magnesium stearate were obtained as a gift sample from Cipla Pharma Pvt Ltd (Mumbai, India).

### 2.2 Preparation of Lamivudine Standard graph

Stock solution of Lamivudine was prepared by using 100 ml volumetric flask. 10 mg of lamivudine dissolved in 25 ml methanol and volume was make up by distilled water. 1 to 12 mcg/mL concentrations were prepared of solutions. The absorbance of above solutions was recorded at max (271 nm) using double beam UV-Visible spectrophotometer. Standard graph was plotted between the concentration (on X-axis) and absorbance (on Y axis).

### 2.3 Compatibility of Lamivudine with drug-polymer

The pure drug and drug-polymer combinations of various physical mixtures were subjected to IR Spectroscopy using Fourier Transform Infrared spectrophotometer (Bruker, Germany). Their spectra were obtained over the wave number range of 4000 – 400 cm<sup>-1</sup>.

### 2.4 Preparation of Lamivudine Matrix Tablets

All the matrix tablets, each containing 150 mg of Lamivudine, were prepared by direct compression and Hot melt granulation technique.

#### 2.4.1 Direct compression method:

The distinct formulations of the matrix tablets analyzed along this study are provided in Table 1. The drug is weighed as per the formula and passed through the sieve no.25 and excipients were weighed as per formula and passed through Sieve no. 40 mesh separately and collected. Ingredients were mixed in geometrical order and thoroughly mixed in a polythene bag for 15 minutes to get a uniform mixture. Magnesium stearate were added to the powder mixture and compressed on a 16- station (single punch, semi automatic, model 999, Shimadzu Corporation, Kyoto, Japan) tablet compression machine using 9.8 mm X 10mm round flat face punch.(Batch no. F001, F002, F003, F004). 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. The total weight of the matrix tablets was 325 mg with different drug polymer ratios like 1:0.25, 1:0.50, and 1:0.75.

#### 2.4.2 Melt granulation method:

The distinct formulations of the matrix tablets analyzed along this study are provided in Table 1. The drug is weighed as per the formula and passed through the sieve no.25 and excipients were weighed as per formula and passed through Sieve no. 40 mesh separately and collected. Glyceryl behenate melted in a porcelain dish over a water bath maintained at 75 °C for 3 min and Lamivudine was gradually added with continuous stirring until uniformly mixed. The molten mixture was allowed to cool and solidify at room temperature crushed in a mortar and passed through a sieve no. 25. The granules were lubricated by magnesium stearate as per quantity in formula and compressed on 16 stations (single punch, semi automatic, model 999, Shimadzu Corporation, Kyoto, Japan) tablet compression machine using 9.8 mm X 10mm round flat face punch at a force of 1 ton.(Batch no. F005, F006, F007, F008) [9, 10].

**Table 1. Composition of different formulations**

Formulation Code	F1	F2	F3	F4	F5	F6	F7	F8
Lamivudine	150	150	150	150	150	150	150	150
Glyceryl behenate	37.5	75	75	112.5	37.5	37.5	75.00	112.5
MCC	126.50	—	—	—	—	—	—	—
Lactose monohydrate	—	89.0	87.00	49.50	126.50	125.00	87.50	50.00
Aerosil	5.00	5.00	5.00	5.00	5.00	6.5	6.5	6.5
Magnesium stearate	6.00	6.00	8.00	8.00	6.00	6.00	6.00	6.00
Total weight of tablet	325.00	325.00	325.00	325.00	325.00	325.00	325.00	325.00

## 2.5 Evaluation of Precompression Blend

Prior to compression, granules were evaluated for their micromeritic parameters. Angle of repose was determined by funnel method. Bulk density (BD) and tapped density (TD) were determined by cylinder method, and Carr's index (CI) was calculated using the following equation

$$CI = (TD - BD) / TD \times 100 \dots \dots \dots (1)$$

Hausner's ratio (HR) was calculated by the following equation

$$HR = TD / BD \dots \dots \dots (2)$$

## 2.6 Physicochemical Evaluation of Matrix Tablets

### 2.6.1. Friability

Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Preweighed randomly selected twenty tablets were placed in a Roche friability tester and operated for 4 min at 25 rpm. Compressed tablets should not lose more than 1% of their weigh. [11]

### 2.6.2. Thickness and diameter

Tablet thickness and diameter were measured by Vernier calipers (Mitatoyo, Japan). [12]

### 2.6.3. Weight variation

A weight variation test was performed according to USP30 NF25 on 20 tablets by taking samples from a batch after production of every 100 tablets and randomly from a total batch of 300 tablets using an electronic balance (Contech Instruments CA 224, India). [13]

### 2.6.4. 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.

### 2.6.5. Drug Content Uniformity

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. Ten tablets were weighed and taken into a mortar and crushed into fine powder. An accurately weighed portion of the powder equivalent to about 150 mg of lamivudine matrix tablet was transferred to a conical flask containing 100ml of pH 0.1N HCl. It was shaken by mechanical means for 24h. Then it was filtered through a Whatman filter paper (No. 1) and appropriate dilutions were made and the absorbance was measured at 280 nm by using double beam UV-VIS spectrophotometer. [14]

### 2.6.6 In -Vitro Drug Release Characteristics

Drug release was assessed by dissolution test under the following conditions: n = 3, USP type II dissolution apparatus (Paddle method) at 75 rpm in 900 mL of 0.1N HCl throughout the dissolution up to 24 hours, maintained at  $37^\circ\text{C} \pm 0.5^\circ\text{C}$ . An aliquot (5mL) was withdrawn at specific time intervals and replaced with the same volume of pre warmed ( $37^\circ\text{C} \pm 0.5^\circ\text{C}$ ) fresh dissolution medium. The samples withdrawn were filtered through Whatman filter paper (No.1) and drug content in each sample was analyzed by UV-visible spectrophotometer at 280 nm. [15]

### 2.6.7 Drug release kinetics

To determine the mechanism of drug release from the formulations, the data were subjected to

Zero-order----- (Eq 1),  
 First order----- (Eq2) and  
 Higuchi ----- (Eq 3) release kinetics

$$M_t = M_0 + k_0t \dots \dots \dots (1)$$

$$\ln M_t = \ln M_0 + k_1t \dots \dots \dots (2)$$

$$M_t = M_0 + k_H t^{1/2} \dots \dots \dots (3)$$

Where  $M_t$  is the cumulative amount of drug released at any time,  $t$ , and  $M_0$  is the dose of the drug incorporated in the delivery system.  $k_0$ ,  $k_1$  and  $k_H$  are rate constants for zero-order, first order and Higuchi models, respectively. The dissolution data were also fitted according to the well-known exponential equation of Peppas as in Eq 4, which is often used to describe drug release behavior from polymeric systems.

$$M_t/M_\infty = k t^n \dots \dots \dots (4)$$

Where,  $M_t/M_\infty$  is the fraction of drug released at time,  $t$ ,  $k$  is the kinetic constant, and  $n$  is the diffusional exponent for drug release. The diffusional exponent,  $n$ , is dependent on the geometry of the device as well as the physical mechanism of release. Zero order release describes a release rate independent of drug concentration while the Higuchi square root kinetic model describes a time dependent release process. The value of  $n$  indicates the drug release mechanism; if  $0.1 < n < 0.5$ , Fickian diffusion is indicated while  $0.5 < n < 1$  indicates non-Fickian diffusion. [16].

### 3. Results and Discussion

#### 3.1 Lamivudine calibration curve

The standard graph of Lamivudine has shown good linearity with R2 value 0.993 in pH 6.8 buffer (Fig-1), which suggests that it obeys the “Beer-Lambert’s law”.

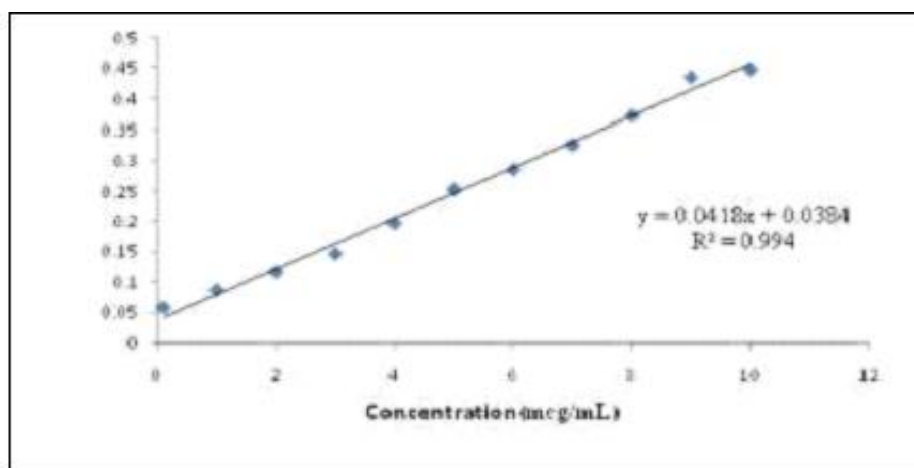


Figure 1. Standard graph of Lamivudine in Methanol

#### 3.2 Fourier Transmission Infra Red (FTIR) Studies

FTIR studies were performed on drug and the optimized formulation using Shimadzu FTIR (Shimadzu Corp., India). The samples were analyzed between wave numbers 4000 and 400 cm<sup>-1</sup>. (Figure-2, 3)

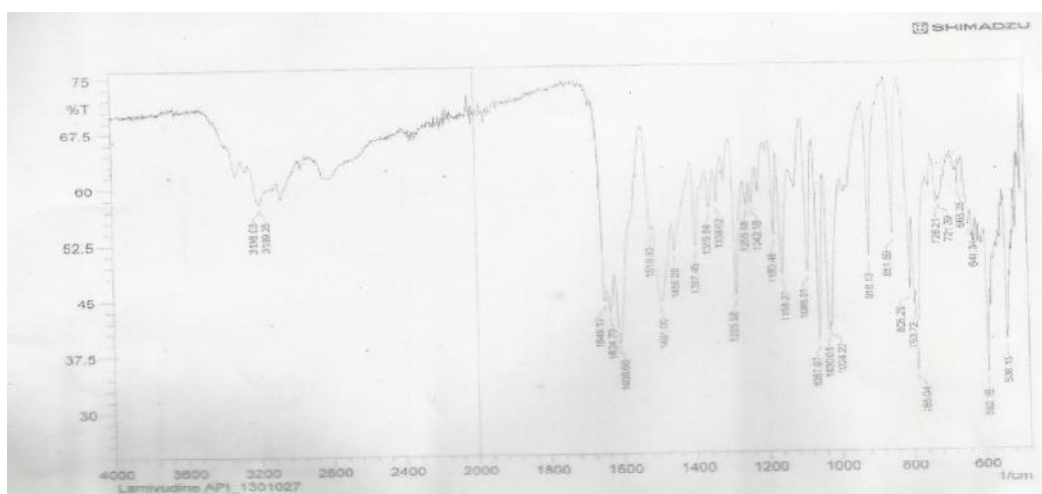


Figure 2. IR Spectra of Lamivudine

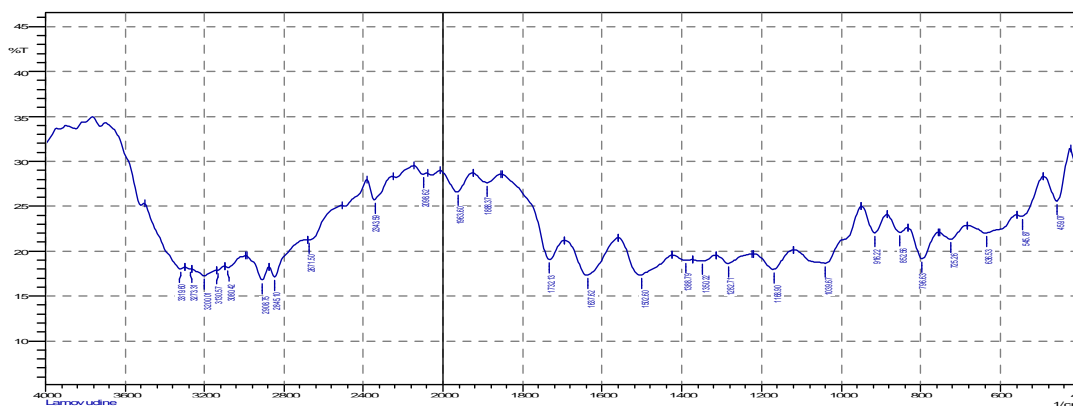


Figure 3. IR Spectra of Lamivudine with Excipients

### 3.3 .Micromeretic properties of granules of different formulations.

The physical mixture for matrix tablets were characterized with respect to angle of repose, bulk density, tapped density, Carr's index, and drug content (Table 2). Angle of repose was less than 25° and Carr's index values were greater than 25 for the powder of all the batches indicating excellent to poor flowability and compressibility. Hausner's ratio was found to be between 1.4 to 1.7 for all the batches indicating that passable to poor flow properties. The drug content was more than 95 % for all the different formulations.

**Table 2. Micromeretic properties of granules of different formulations**

Formulation Code	Bulk Density	Tapped Density	Hausner's Ratio	Compressibility Index	Angle of repose
F001	0.495	0.625	1.26	20.8	35 ± 0.65
F002	0.523	0.689	1.31	24	40 ± 0.72
F003	0.512	0.625	1.22	18	37 ± 0.77
F004	0.521	0.671	1.28	22	28 ± 0.29
F005	0.515	0.662	1.28	22	33 ± 0.81
F006	0.588	0.659	1.12	10.77	30 ± 0.72
F007	0.595	0.675	1.13	13.44	38 ± 0.65
F008	0.591	0.681	1.11	9.00	38 ± 0.65

\*All values are expressed as mean ± S.D,

### 3.4 Physicochemical characterization of Tablets

The results of the uniformity of weight, hardness, thickness, friability, and drug content of the Tablets are given in (Table 3). All the tablets of different batches complied with the official requirements of uniformity of weight as their weights varied between 308.75 mg and 341.2mg (±5%) The hardness of the tablets ranged from 7.00 to 10.00kg/cm<sup>2</sup> and the friability values were less than 0.8% indicating that the matrix tablets were compact and hard. The thickness of the tablets ranged from 6.80 to 7.25 mm. All the formulations satisfied the content of the drug as they contained 95 to 99 % of Lamivudine and good uniformity in drug content was observed. Thus all the physical attributes of the prepared tablets were found to be practically within control.

**Table 3. Physicochemical characterization of Tablets**

Formulation Code	Average Weight (mg)	Thickness (mm)	Hardness (Kg/cm <sup>2</sup> )	Friability(%)
F001	324.85±4.53	6.79±0.05	9±0.458	0.10%
F002	328.23±5.31	7.12±0.04	8±0.435	0.18%
F003	322.56±2.56	6.89±0.07	8.1±0.519	0.15%
F004	324.34±3.43	6.77±0.02	7.766±0.65	0.14%
F005	324.27±3.57	7.21±0.06	8.35±0.535	0.16%
F006	324.63±2.45	6.84±0.09	7±0.5	0.19%
F007	324.52±4.12	6.87±0.07	9.133±0.50	0.19%
F008	325.73±4.23	6.91±0.13	8.74±0.329	0.12%

\*All values are expressed as mean ± S.D.

### 3.5 In vitro drug release

The drug release data are shown in Table 4. Expectedly, drug release from the tablets Prepared by melt granulation were 78.85±0.98%, 72.25±0.19% and 66.78±1.02 after 12 h for formulations F006, F007, and F008 respectively, thus indicating that drug release fall as the glyceryl behenate content of the tablets increased. The difference in release rate between the batches was statistically significant (p < 0.05). Furthermore, comparison of the two methods of formulation used indicate that cumulative release from the tablets prepared by direct compression (F002, 86.80 %) was significantly higher (p < 0.05) than from the equivalent formulation made by melt granulation (F008, 66.78 %)

**Table 4. Dissolution Profile (% drug release) of different formulations at different time points.**

Time (hr)	% of Drug Release							
	F001	F002	F003	F004	F005	F006	F007	F008
0	0	0	0	0	0	0	0	0
2	28.66±1.25	25.42±1.04	24.22±1.17	21.34±1.15	26.49±1.02	25.69±1.13	20.42±1.11	19.44±0.99
4	40.63±1.30	35.63±1.23	34.83±1.11	30.65±1.08	36.59±1.07	35.85±1.15	31.65±1.05	29.39±1.10
6	52.49±0.92	45.72±0.92	45.43±0.95	40.72±0.93	47.41±0.93	48.70±0.97	40.45±0.81	39.46±0.83
8	64.37±1.15	58.45±0.87	56.56±0.80	49.73±0.90	57.68±1.11	58.43±1.06	49.35±0.92	49.50±1.10
10	76.42±0.87	74.12±0.80	73.14±0.78	60.14±0.74	68.61±0.81	69.52±0.97	61.45±0.97	57.51±0.85
12	86.80±0.45	80.45±1.11	78.12±0.98	74.14±0.16	80.67±0.15	78.85±0.98	72.25±0.19	66.78±1.02

\*All values are expressed as mean ± S.D

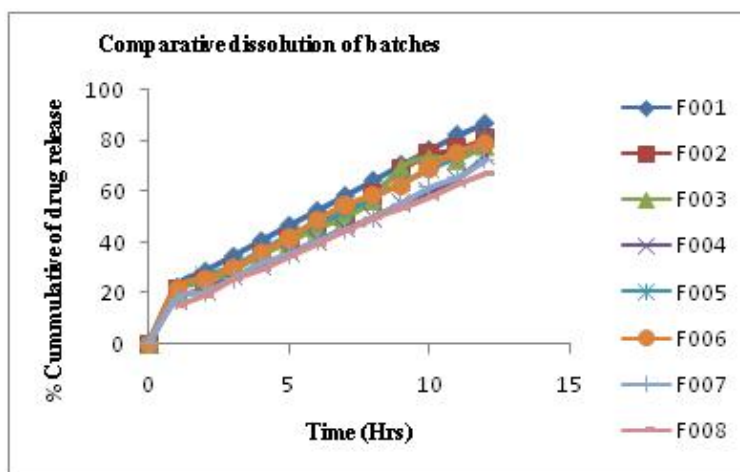
### 3.6 Drug release kinetics

Table 5 shows that the best-fit release kinetic data with the highest values of regression

Coefficient ( $R^2$ ) was shown by zero order and Higuchi models. Zero order release describes the release rate independent of drug concentration. Higuchi square root kinetic model describes, release drug from the insoluble matrix as square of time dependant process. It describes release of drug by simple diffusion mechanism. The values of  $n$  were in the range of 0.5531 to 0.7166 (i.e., more than 0.5) indicating non-Fickian release (diffusion controlled).  $R^2$  data indicate that Higuchi and Peppas models also suitably described the release of Lamivudine from the matrix tablets.

**Table 5. Kinetic Values Obtained from Different Plots of Formulations**

Formulation Code	Zero order	First order	Higuchi	Korsmeyer and Peppas	
	$R^2$	$R^2$	$R^2$	$n$	$R^2$
F001	0.9580±0.012	0.8580±0.005	0.9580±0.0033	0.5679	0.9780±0.064
F002	0.9967±0.022	0.897±0.0	0.9468±0.081	0.5903	0.9680±0.0115
F003	0.9985±0.007	0.9085±0.004	0.95185±0.0040	0.6670	0.9804±0.0087
F004	0.9952±0.003	0.9152±0.004	0.9752±0.0026	0.5639	0.9801±0.0046
F005	0.9675±0.004	0.8975±0.006	0.9875±0.0036	0.5616	0.9747±0.0038
F006	0.9635±0.001	0.9154±0.0034	0.9834±0.0070	0.6203	0.9818±0.0038
F007	0.9876±0.003	0.9276±0.004	0.9843±0.007	0.7075	0.9762±0.0070
F008	0.9996±0.001	0.9446±0.008	0.9916±0.008	0.7164	0.9815±0.0054

**Figure 4. Comparative Drug release profile of all Batches**

### 3.7 Effect of concentration of the glyceryl behenate matrix on drug release

During preliminary studies (not reported here), it was observed that at low concentrations of the glyceryl behenate the matrices of the tablets readily disintegrated during dissolution test. Disintegration properties of these matrices were depending on content of matrix forming agent. Hence different ratios of drug: Lipophilic binders were to prepare matrices and drug release retardation. This was not, however, the case when the content of the matrix former was increased, thus indicating that a minimum of level of the glyceryl behenate is required to form a proper matrix that would not readily disintegrate. This may be due to slower penetration of the dissolution medium into the waxy

matrices i.e. increasing the ratio of drug: lipophilic binder from 1:0.25, 1:0.50, 1:0.75 resulting decrease release of drug. In all formulation F008 shows maximum drug release retardation because of high concentration of polymer in the ratio of 1:0.75 i.e.  $66.78 \pm 1.02\%$ . From figure 4 it can be observed that for all the matrices drug release is inversely proportional to level of rate retarding matrix former present in the matrix system i.e. the rate and extent of drug release decrease with increase in total lipid content of matrix. Lamivudinne release occurred by different mechanism diffusion or erosion depending on lipid binder used. Increasing the ratio of glyceryl behenate in granules resulted in decreasing the release of drug. As stated earlier, based on kinetic analysis of release data, Lamivudine release occurred by a non- Fickian diffusion mechanism. The initial drug release (i.e., in the 1st hour) of  $15.44 \pm 1.21\%$  and after 12 h  $66.78 \pm 1.02$  respectively of batch F008.

### 3.8 Effect of method of tablet preparation on drug release

Figure 5 compares the release profiles of tablets prepared by melt granulation and direct compression methods, respectively. Both cumulative drug release and drug release rates were higher for the matrix tablets made by direct compression of physical mixtures (F001) than for the tablets obtained by the compression of granules made by melt granulation (F008) This can be attributed to the formation of a more uniform and, therefore, more effective coating of the glyceryl behenate matrix around the drug particles in the tablets prepared by melt granulation technique than in those made by direct compression. Thus the tablets made by the former technique are likely to show greater integrity. Consequently, while the probable mechanism of drug release from the direct compressed-matrix tablets is erosion control, drug release from melt granulated tablets would likely be diffusion-controlled as confirmed by the kinetic data in Table 5. All the parameters were run 3 times (n=3).The difference in the mean of % Cumulative drug release between batch F008 and F001, F002,F003 was significant ( $p < 0.05$ )

Melt granulation > physical mixture

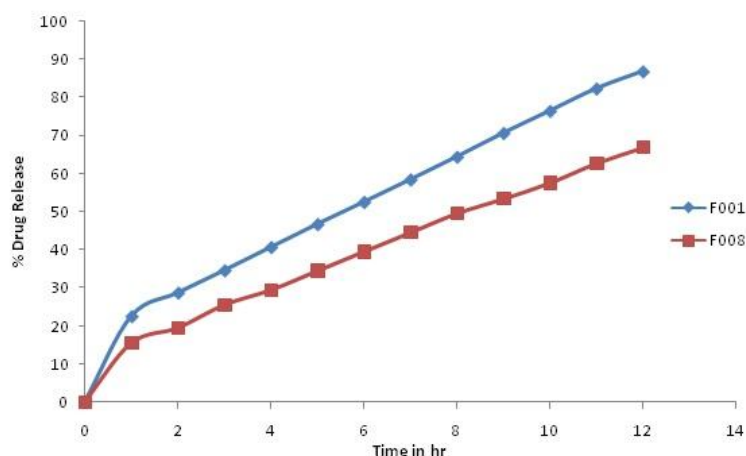


Figure 5. Comparative Drug release profile of batches showing effect of method preparation of matrix tablet

## 4. Conclusion

From preformulation studies, it was found that the sample of lamivudine is pure and suitable drug candidate for formulation of lipophilic matrix tablets. From compatibility studies it was no evidence of interaction between drug and polymer and polymer is suitable for preparation of matrices of highly water soluble drug. From pre-compression studies it was concluded that all the parameters passes the standards and the granules are suitable for preparation of lamivudine matrix. From post-compression studies it was concluded that all the parameters passes the standards and the melt granulation method was suitable for preparation of lamivudine matrices. From the in-vitro release study it was concluded that as the concentration of compritol 888 is increased, the drug release rate was decreased. Both cumulative drug release and drug release rates were higher for the matrix tablets made by direct compression of physical mixtures than for the tablets obtained by the compression of granules made by melt granulation. Overall the curves fitting into various kinetic models confirmed that in-vitro release kinetics of all formulations was best fitted into Zero order model and Higuchi model. The n values more than 0.5 indicates that the mechanism in which the drug release from matrices follow non-fickian diffusion mechanism. The developed Lamivudine matrix tablets prepared by melt granulation may be used clinically for prolonged drug release for at least 24 h.

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