Pharma Health SciencES

International Journal of Pharma Research and Health Sciences

Available online at www.pharmahealthsciences.net

Original Article

Formulation and *In-vitro* Evaluation of Matrix Controlled Lamivudine Tablets

Harekrishna Roy [1,*], Sanjay Kumar Panda [2], Kirti Ranjan Parida [3], Asim Kumar Biswal [4]

[1] Department of Pharmatechnology, Vikas College of Pharmaceutical sciences, Suryapet, Nalgonda, Andhra Pradesh, India.

[2] Genovo development services ltd., Bangalore, India.

[3] Department of Pharmatechnology, Jeypore college of pharmacy, Rondapalli,Odisha, India.

[4] Formulation Research & development, FDC Limited, Mumbai, India.

ARTICLE INFO

Received: 1 Nov 2013

Accepted: 5 Dec 2013

Key words:

Hypromellose, Lamivudine, Matrix-controlled, Micromeritic, Higuchi

ABSTRACT

Aim: The current paper was an attempt to design a sustained release dosage form using various grades of hydrophilic polymers, Hypromellose (hydroxyl-propyl methylcellulose HPMC K4M, HPMC K15M and HPMC K100M) and Povidone K30 as binder solution in a matrix-controlled drug delivery system of Lamivudine. *Materials and Methods*: Laboratory scale batches of six tablet formulations were prepared by wet granulation technique. Micromeritic properties of the granules were evaluated prior to compression. Tablets were characterized as crushing strength, friability, weight variation, thickness, drug content or assay and evaluated for *in-vitro* release pattern for 24 h using buffer (P^H-1.2) followed by Phosphate buffer of pH 6.8 at 37 ± 0.5°C. The *in-vitro* release mechanism was evaluated by kinetic modeling. *Results and Discussion*: The results obtained revealed that HPMC K4M at a concentration of 25% in formulation (F2) was able to sustain the drug release for 24 h and followed the Higuchi pattern. There was no such major chemical interaction found between the drug and excipients during Fourier Transform Infrared Spectroscopy (FTIR) study. *Conclusion*: Hence, combinely HPMC K4M and Povidone K30 at a suitable concentration can effectively be used to sustain drug release.

Corresponding author *

E-mail address:hareroy@gmail.com (Harekrishna Roy)

1. INTRODUCTION

Oral route is the most preferred route for administration of drugs. Among all tablets are the most popular oral formulations available and preferred by the patients and physicians alike.[1] In long-term therapy for the treatment of chronic disease conditions, conventional formulations are required to be administered in multiple doses, and therefore have several disadvantages. Hence, Controlled release (CR) tablet formulations are much desirable and preferred for such therapy because they offer better patient compliance, maintain uniform drug levels, reduce dose and side effects, and increase safety margin for high potency drugs.[2, 3]

Human immune deficiency virus (HIV) is a retrovirus that can lead to *acquired immunodeficiency syndrome* (AIDS), a condition in humans in which the immune system begins to fail, leading to life threatening opportunistic infections. There are two type of HIV(HIV-1 and HIV-2) and both are infectious and causing agent of AIDS. Development of disease results from lack of control of HIV replication by the host immune system. a person acquires aids after the HIV infection has damaged the immune system to a point (less than 200 CD4+ lymphocytes per microlitre of blood) that a body can no longer protect itselffrom other infections and cancers. Though there are no such drug available to cure from such disease, the progress of disease can be slow down by several drug. Out of them Lamivudine is a class of drug under nucleoside reverse transcriptase inhibitors (NRTIs). [4, 5]

Lamivudine chemically known as 4-amino-1-[(2*R*,5*S*)-2-(hydroxymethyl)-1,3-oxathiolan-5yl]1,2-dihydropyrimidin-2-one, category of drug under NRTIs. It phosphorylate and active 5'-triphosphate metabolite, inhibits the HIV reverse transcriptase enzyme competitively. It has absolute bioavailability of 90% with terminal half life of 5-7 hours. But some serious adverse effects like liver damage, nausea, stomach pain, low fever, loss of appetite, dark urine, clay-colored stools, and jaundice are associated with frequent administration of dose. [6] Hence, during the study an attempt has been made to design matrix controlled delivery system using various grades of hypromellose (HPMC K4M, HPMC K15M and HPMC K100M).[7]

2. MATERIALS AND METHODS

2.1 Materials

Lamivudine was procured as gift sample from cipla Ltd, Mumbai, India. Hypromellose (HPMC K4M, HPMC K15M and HPMC K100M) were purchased from Signet chemical corporation Mumbai, India. Povidone K30 was purchased from Orchid Healthcare, Chennai, India. Dicalcium phosphate, Talc and Magnesium stearate were procured from SD Fine chemicals, Mumbai, India. Colloidal silicon dioxide (Aerosil) was purchased from Tangmin industry Ltd, China. All chemicals and solvents used are of high analytical grade.

2.2 Method of Preparation of Matrix Tablets

Lamivudine, HPMC K4M, HPMC K15M, HPMC K100M, dicalcium phosphate, Povidone K30 were passed through #40 mesh and collected separately in a polyethylene bag. Wet granulation technique was applied for the batch preparation of matrix tablets. All the materials were sifted to rapid mixing granulator and mixed for 20 min at optimized speed. Povidone K30 was dissolved in hot water with the help of a mechanical stirrer. The above binder solution was added to dry mix and mixed for 15 min to get wet mass. Then, the resultant wet mass was dried at inlet temperature of 40°C to 55°C for 60 min and passed through multi mill (Propack Techno Pvt. Ltd, India). The resultant dried granules were sifted through #20 mesh and milled through multi mill. The comminuted

granules were lubricated with Aerosil, Magnesium stearate and talc which was already passed through for 10 min in Octagonal Blender (Mevish engineering, India). Finally, the lubricated granules were compressed to formulate tablets using a tablet compression machine (Cadmach Machinery Pvt. Ltd, India) with 12 mm flat punch. [8, 9]

Table 1: Formulation of Lamivudine matrix tablets

	Formulation					
Quantity (mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Lamivudine	150	150	150	150	150	150
Dicalcium Phosphate	150	200	250	150	200	250
HPMC K4M	100	150	-	-	-	-
HPMC K15M	-	-	100	150	-	-
HPMC K100M	-	-	-	-	100	150
Povidone K30	200	100	100	150	150	50
Aerosil	1	1	1	1	1	1
Talc	1	1	1	1	1	1
Magnesium Stearate	1	1	1	1	1	1
Total weight (mg)	**603**	**603**	**603**	**603**	**603**	**603**

2.3 Micromeritic properties of blended powder

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

$$CI = (TD-BD)/TD \times 100 \quad \text{..... (1)}$$

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

$$HR = TD/BD \quad \text{..... (2)}$$

Table 2: Micromeritic properties of Preparedgranules

Formulations	Bulk density	Tapped density	Angle of repose	Hausner´s ratio	Carr´s index
F1	0.68±0.09	0.74±0.92	30.72±1.11	1.08	8.1
F2	0.72±0.28	0.79±1.09	32.13±1.03	1.09	8.86
F3	0.69±0.34	0.74±1.41	33.25±1.26	1.07	6.75
F4	0.71±0.51	0.79±0.73	34.31±1.25	1.11	10.12
F5	0.73±0.44	0.81±1.03	33.46±1.27	1.1	9.87
F6	0.69±0.34	0.77±0.42	32.47±1.46	1.16	10.38

Data are represented as mean ± standard deviation (SD),n=3

2.4 Physiochemical characterization of Tablets

The physical properties such as *crushing strength, friability, thickness, diameter, weight variation, drug content* for each formulation were determined.

Crushing strength.

Tablet crushing strength was determined by randomly selected 10 tablets using a digital crushing strength tester and the data reported is the mean of three individual determinations. [10]

Table 3: Physiochemical characterization of Prepared tablets

	F1	F2	F3	F4	F5	F6
Crushing strength (Newton)	79.8±1.54	70.4±2.73	80.51±2.71	75.39±1.95	80.7±1.26	76.64±2.76
Friability (% w/w)	0.5±0.04	0.38±0.03	0.51±0.07	0.49±0.07	0.29±0.18	0.49±0.78
Thickness (mm)	2.42±0.28	2.43±0.37	2.42±1.03	2.42±0.22	2.42±0.04	2.42±0.17
Diameter (mm)	12.00±0.06	12.00±0.05	12.00±0.02	12.00±0.023	12.00±0.01	12.00±0.03
Weight variation (mg)	603.2±1.31	603.3±1.22	603.7±1.47	604.2±2.12	602.98±2.43	603.9±2.06
Drug content(%)	101.28±2.13	100.43±1.78	99.48±2.76	99.98±1.69	100.47±2.36	100.97±2.23

Data are represented as mean ± standard deviation (SD),n=3

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]

Thickness and diameter.

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

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]

Drug content.

The drug content in terms of assay of each batch was determined in triplicate. For each batch a number of 20 tablets were weighed and crushed to fine powder using mortar and pestle. An accurately weighed of 10 mg of the powder was taken and suitably dissolved in methanol and analyzed by HPLC after making appropriate dilutions. The procedure was carried out on Shimadzu LD-10AT with flow rate of 2.0 ml/minute at ambient temperature. [14]

2.5 In-vitro dissolution study

The procedure was determined using United States Pharmacopoeia (USP) XXIV dissolution testing apparatus II (paddle method). The dissolution test was performed using 900 ml of 0.1N HCl (pH-1.2) at 37 ± 0.5°C and followed by Phosphate buffer (P^H 6.8) at 50 rpm for a period of 24 hours. A sample of 10 ml of the solution was withdrawn from the dissolution apparatus at 10 minute interval with the replacement of fresh dissolution medium for 20 minute. The samples were passed through a 0.45 μm membrane filter and diluted to a suitable concentration with phosphate buffer. The absorbance of these solutions was measured at 271 nm using a Shimadzu UV-1601 UV/Vis double beam spectrophotometer.[15]

3. RESULTS AND DISCUSSION

3.1 Micromeritic properties of granules

Result shows that all the formulations produced optimal flow properties calculated in terms of compressibility. Table 2 depicts micromeritic properties of the designed formulations. The angle of repose ranged from 30.72±1.11 to 34.31 ± 1.25 which indicates optimal flow ability. In addition to that the tapped density and bulk density for all formulation granules ranged between 0.74±0.92 to 0.81±1.03 and 0.68±0.09 to 0.73±0.44 respectively, whereas Hausner's ratio was obtained between 1.07 to 1.16.

3.2 Physiochemical characterization of Tablets

The physical properties of the designed tablets are presented in Table 3. These properties were studied by determining crushing strength, friability, thickness, diameter, weight variation and drug content. Crushing strength of prepared tablets ranged from 70.4±2.73 newton to 80.7±1.26 newton. It was observed that those formulations contained HPMC K100M exhibited higher hardness than others. The reason may be the highest molecular weight compared to rest hypromellose. Morever, the presence of hypromellose at 60% in all formulations showed higher crushing strength. The European and United States Pharmacopeia state that a loss up to 1% is acceptable for friability. Prepared tablets passed the friability test as values were ranged from 0.29% to 0.51% indicating the ability of tablet to withstand abrasion in handling packaging and shipment. The thickness for all tablets ranged between 2.42±0.17 to 2.43±0.37 mm and diameter was similar for all tablets. In a weight variation test, the pharmacopoeial limit for the percentage deviation for tablets of more than 325 mg is ±5 %. The average percentage deviation of all tablet formulations was found to be within the above limit and hence all formulations passed the test for uniformity of weight as per official requirements. Average weight of each formulation tablets ranged from 602 mg to 603 mg. Uniformity in drug content was found among different formulations of the tablets, and the percentage of drug content was more than 99% in all cases.

3.3 In-vitro dissolution study

Different grades of Hypromellose ranging 16 and 25 percentages were used to formulate matrix tablets and those formulations were subjected to *in-vitro* drug dissolution studies. All formulation released 19% of

drug within 2 hours. Formulations based on HPMC K4M at 16 and 25% level showed complete release within 24 hours whereas HPMC K15M and HPMC K100M based formulations released maximum of 80% drug and complete 100 % drug release within 24 hours. Result showed that HPMC K15M based formulations exhibited slower drug release among all hypromellose. Whereas, HPMC K4M was able to deliver 100% drug release in 24 hours. To confirm the promising formulation, release data were subjected different release kinetics. Result revealed all formulation obeyed higuchi pattern and highest R^2 value of 0.9939 for F2 formulation. Hence on the basis of above result, F2 was selected as promising formulation for further studies.

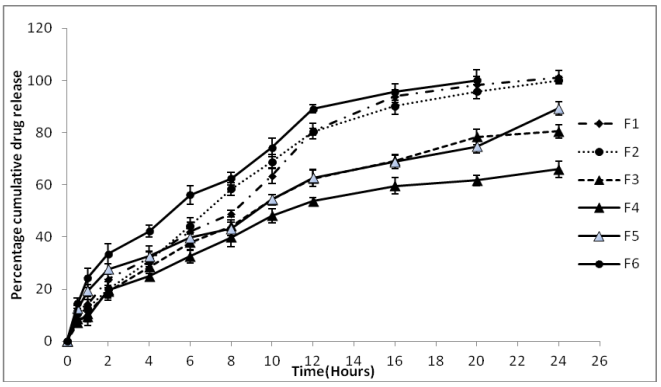

Fig 1: In-vitro release profile of formulations

3.4 Drug polymer interaction study

The drug - excipient interaction were studied using FTIR (FTIR 8400S, Schimazu). IR spectra for drug and powdered tablets were recorded in a Fourier transform infrared spectrophotometer with KBr pellets. The spectra were scanned over 3600-400 cm-1 range. It was found that there was no chemical interaction between pure drug and excipients used as cited in figures 2 and 3. [16]

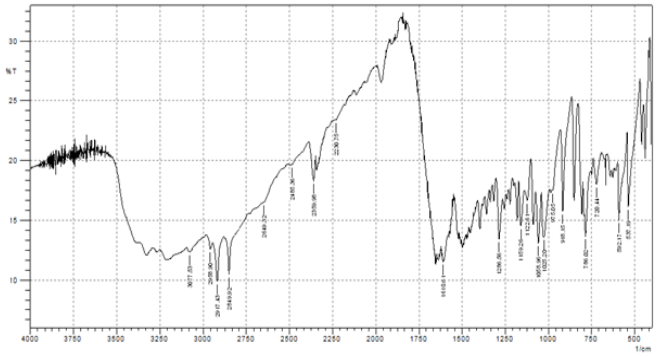

Fig 2: FTIR spectrum of Lamivudine

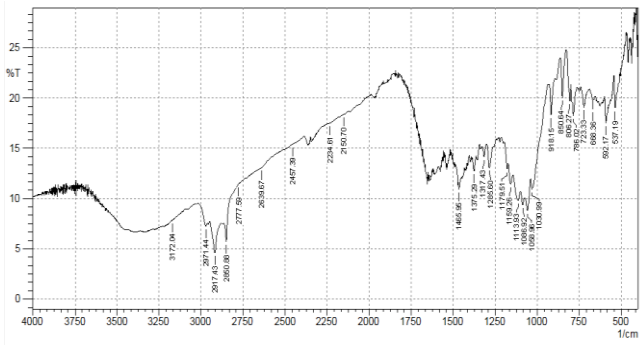

Fig 3: FTIR Spectrum of best batch (F2)

3.5 Stability study of best batch

Long term, intermediate and accelerated stability testing were carried out based on the ICH guidelines considering 25±2°C/60±5% RH, 30±2°C/65±5% RH and 40±2°C/75±5% RH respectively. One hundred tablets of batch F2 were securely packed in aluminium blister and placed in humidity chamber. The samples were evaluated for crushing strength and drug assay at a regular interval of 3 months during the study of 24 month. There was no significance change in crushing strength and drug assay as shown in Table 4. Thus, F3 formulation batch confirmed its stability.

Table 4: stability study of best batch

Long term stability study (25± 2°C & 60±5% RH)				
Days (Month)	**3**	**6**	**9**	**12**
Drug assay (%)	100.39± 0.91	100.19± 2.13	101.22± 2.04	101.35± 2.42
Crushing strength (newton)	70.4±2. 25	70.16±2 .18	69.67±2 .47	70.33±1 .53
Intermediate stability (30± 2°C & 65±5% RH)				
Days (Month)	**3**	**6**	**9**	**12**
Drug assay (%)	101.27± 1.45	100.31± 2.42	100.28± 2.17	99.67±1 .56
Crushing strength (newton)	70.19±2 .45	70.48±1 .42	69.27±2 .02	69.48±1 .46
Accelerated stability (40± 2°C & 75±5% RH)				
Days (Month)	**1**	**2**	**3**	**6**
Drug assay (%)	99.25±2 .17	100.08± 2.04	99.02±2 .88	100.47± 2.58

Crushing strength (newton)	70.57±2 .1	70.18±1 .26	70.06±2 .17	69.09±2 .37

Data are represented as mean ± standard deviation (SD),n=3

4. CONCLUSION

The present investigation shows that the various hypromellose can effectively be used to design matrix tablet of Lamivudine utilizing wet granulation technique. The use of hypromellose with suitable combination of binder (Povidone K30) for preparation of matrix is highly effective and commercially feasible. The physiochemical characterizations of all formulations were found to be satisfactory. Result shows formulation F2 based on HPMC K4M exhibited prolong drug release within 24 hour. From dissolution study F2 was selected as best laboratory scale grade batch. Hence reproducible production scale batches of size 1000 tablets were designed and charged for stability study. Parameters were checked and found to be within the specified limit. Furthermore the *in-vivo* and pharmacokinetic study have to carry out.

5. ACKNOWLEDGMENTS

Authors wish to thanks faculties of Vikas College of pharmaceutical sciences, Jeypore college of pharmacy and formulation and research development team (FDC limited, Mumbai).

6. REFERENCES

1. Chien YW. Concepts and system design for Rate-controlled drug delivery. In: Novel Drug Delivery Systems. 2nd ed. New York: Marcel Dekker; 1992. 1-38.

2. Singh BN, Kim KH. Floating drug delivery systems: An approach to oral controlled drug delivery via gastric retention. J Control Release 2000;63: 235-59.

3. Brazel CS, Peppas NA. Temperature-and pH-sensitive hydrogels for controlled release of antithrombotic agents. Mater Res Soc Symp Proc 1994;331: 211-6.

4. Dragsted UB, Gerstoft J, Pedersen C. Randomized trial to evaluate indinavir/ritonavir versus saquinavir/ritonavir in human immunodeficiency virus type 1-infected patients: the MaxCmin 1 Trial. J Infect Dis 2003; 188: 635-642.

5. Cohen Stuart JW, Schuurman R, Burger DM. Randomized trial comparing saquinavir soft gelatin capsules versus indinavir as part of triple therapy (CHEESE study). *AIDS* 1999;13: F53-58

6. Ravi PR, Ganga S, Saha RN. Design and Study of Lamivudine Oral Controlled Release Tablets. AAPS PharmSciTech, 2007; 8(4): 101-113.

7. Tiwari SB, Murthy TK, Pai MR, Mehta PR, Chowdary PB. Controlled release formulation of tramadol hydrochloride using hydrophilic and hydrophobic matrix system. AAPS PharmSciTech 2003;4: E31.

8. Shah S, Shah K, Jan SU, Ahmad K, Rehman A, Hussain A. Formulation and *in vitro* evaluation of ofloxacin-ethocel controlled release matrix tablets prepared by wet granulation method: Influence of co-excipients on drug release rates. Pak J Pharm Sci 2011;24 : 255-61.

9. Gohel MC and Panchal MK. Formulation optimization of diltiazem HCl matrix tablets containing modified guar gum using a central composite design. Pharm Pharmacol Commun 1999; 5: 331-338.

10. Chandrasekhar R, Hassan Z, Alhusban B, Smith AM, Mohammad AR. The role of formulation excipients in the development of lyophilised fast-

disintegrating tablets. Eur J Pharm Biopharm 2009;72: 119-29.

11. Gohel MC, Parikh RK, Brahmbhatt BK, Shah AR. Preparation and assessment of novel coprocessed superdisintegrant consisting of crospovidone and sodium starch glycolate: a technical note. AAPS PharmSciTech 2007; 8:9.

12. Fukami J, Yonemochi B, Yoshihashi Y, Terada K. Evaluation of rapidly disintegrating tablets containing glycine and carboxymethylcellulose. Int J Pharm 2006; 310: 101-9.

13. Madgulkar AR, Bhalekar MR, Padalkar RR. Formulation design and optimization of novel taste masked mouth-dissolvingtablets of tramadol having adequate mechanical strength. AAPS PharmSciTech 2009; 10: 574-81.

14. Hamdani J, Moës AJ, Amighi K. Physical and thermal characterisation of Precirol and Compritol as lipophilic glycerides used for the preparation of controlled‐release matrix pellets. Int J Pharm 2003; 260:47‐57.

15. Ritger PL, Peppas NA. A simple equation for description of solute release, II: Fickian and anomalous release from swellable devices. J Control Rel 1987; 5:37‐42.

16. Sato H, Miyagawa Y, Okabe T, Miyajima M, Sunada H. Dissolution mechanism of diclofenac sodium from wax matrix granules. J Pharm Sci 1997; 86:929‐34.