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FORMULATION AND INVITRO EVALUATION OF LAMIVUDINE FLOATING TABLETS

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ABSTRACT

Lamivudine comes under class II drugs according to BCS classification. It is poorly water soluble drug. It has maximum solubility in pH 1.2 and therefore it will be beneficial to retain the drug in stomach for longer period of time for better absorption. It has been reported that conventional release of Lamivudine in stomach causes stomach pain as a side effect. Hence it was found necessary to develop a gastric retentive dosage form containing lamivudine in order to increase the gastric residence time to enhance its absorption and their by its oral bio availability. Also the slow release of the drug in stomach may avoid the stomach pain associated with immediate release of the drug. The aim of our present study was to design, develop and optimize the floating tablets containing lamivudine in order to increase its gastric retention time for enhancing absorption in stomach as well as to produce a controlled release of the drug for a longer time using polymers such as Carbopol, HPMC and Eudragit S100.

KEYWORDS: Carbopol, HPMC and Eudragit S100.

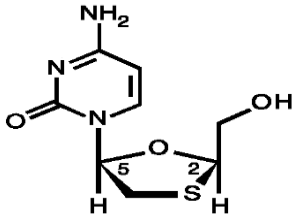
Drug Profile

Lamivudine[41]

Chemical IUPAC name: (2R, cis) – 4 – amino – 1-(2 – hydroxy methy -1, 3-oxathiolan – 5 – yl) – (1H)-pyrimidin – 2 – one.

Empirical Formula: $C_8H_{11}N_3O_3$

Structural formula



Description: Lamivudine is a white to off – white crystalline solid with a solubility of approximately 70µg/ml in water at 25°c.

Bioavailability: 86%

Half Life: 5-7hrs

Mechanism of Action

Lamivudine was originally developed as an antiretroviral drug. The drug is metabolised intracellularly to active triphosphate moiety by both infected and uninfected cells. Lamivudine triphosphote act as a substrate for HBV polymerase. The formation of further viral DNA is blocked by incorporation of lamivudine triphosphate into the viral chain and be subsequent chain termination. Lamivudine triphosphate does not interfere with normal cellular DNA metabolism.

Metabolism

Metabolism of lamivudine is minor route of elimination. In man, the only known metabolism of lamivudine is the trans – sulfoxide metabolite. Within 12 hours after a single oral dose of lamivudine in 6 HIV-1-infected adults, 5.2%± 1.4% (mean + SD) of the dose was excreted as the trans – sulfoxide metabolite in the urine. Serum concentration of this metabolite have not been determined.

MATERIALS AND METHODS

Instruments used

Instruments	Supplier/ Manufacturer
Single pan analytical balance	Amandi , Mumbai
Tablet punching machine	Rimek 12, Ahmedabad
Hardness tester	Lab India
Roche friabilator	Lab India
Dissolution apparatus	Lab India
Disintegration apparatus	Campbell electronics – Mumbai
UV spectrophotometer	Schimadzu

Materials used

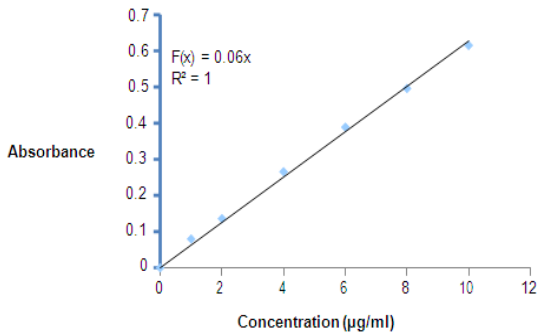
Material	Supplier/ Manufacturer
Lamivudine	Microlabs
HPMC	Lobachemie pvt. Ltd
Eudragit S 100	SD fine chemicals , Mumbai
Carbopol	Ranbaxy chemicals pvt.ltd
Sodium bicarbonate	Qualivens fine chemicals
Magnesium stearate	Lobachemicalse pvt. Ltd
Microcrystalline cellulose	SD fine chemicals
Starch	SD fine chemicals
Talc	SD fine chemicals

RESULTS AND DISCUSSION CALIBRATION CURVE OF LAMIVUDINE

Calibration Data of Lamivudine

Concentration (ug/ml)	adsorbance
0.	0
1.	0.0791
2.	0.1353
4.	0.2656
6.	0.3884
8.	0.4961
10.	0.6153

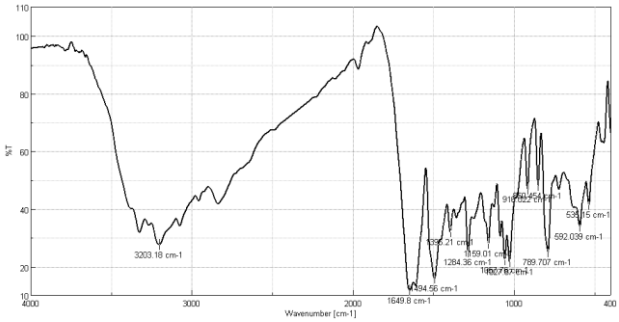
Calibration curve of lamivudine in 0.1N HCl at 280nm



A calibration curve for lamivudine was constructed in 0.1N HCl by scanning the diluted drug solution at 280nm using UV spectrophotometer. The linearity of the calibration curve was found to be in the range of 1-10µg/ml. A regression coefficient value of 0.997 was noticed for lamivudine.

Compatibility studies

IR spectra matching approach was used for detection of any possible chemical interaction between drug and polymer. A physical mixture (1:1) of drug and polymer was prepared and mixed with the suitable quantity of potassium bromide. About 100mg of mixture was compressed to form a transparent pellet using a hydraulic press at 6tons pressure .It was scanned from 4000 to 400 cm-1 in FTIR spectrometer. The IR spectrum of the physical mixture was compared with those of pure and polymers and matching was done to detect any appearance or disappearance of peaks. The IR spectrums of the sample and of the Lamivudine working/reference standard in the range of 4000 cm-1 to 400 cm-1 were taken by preparing dispersion in dry potassium bromide.



IR Spectra of Lamivudine

SUMMARY

The present study was aimed at preparing floating tablet containing Lamivudine for sustained release of drug and study the effect of swellable polymer, release retardant polymer on rate of release and floating lag time. Lamivudine is more soluble in acidic pH and hence it will be beneficial to increase its gastric residence time in order to improve its oral absorption as well as by controlling the release rate, the side effects associated with burst release of the drug can be eliminated.

Formulation

In this study, Carbopol and HPMC were chosen as the swellable polymer and Eudragit S100 was chosen as release retardant polymer. A total of 9 formulations were made with Carbopol and Eudragit S100 combination at three different proportions. Another set of 9 formualtions were made using HPMC and Eudragit S100 combination. Carbopol and HPMC were used in the range of 60, 90 and 120mg, whereas Eudragit S100 was used at the level of 0, 30 and 60mg.

Preformulation Studies

Preformulation studies of the prepared powder blend of all the 18 formulations were performed. Parameters

like angle of repose, bulk density, tapped density, compressibility index, hausner's ratio and swelling studies for the polymers were studied. The results obtained from the above studies showed that the prepared blend was having satisfactory fluidity and compressibility and hence can be processed into tablets by direct compression method. The swelling studies also proved that the chosen polymers have sufficient swelling capacity in order to use them in floating drug delivery systems.

Compression of Tablets

Tablets were compressed by direct compression method using Ribek Tablet punching machine to target weight of about 370mg. All the tablets prepared were having uniform size and thickness with a hardness of about 2-5kg/cm. There was no processing problems encountered during the compression process.

Evaluation of Tablets

The compressed tablets were then evaluated for various tests like hardness, weight variation, content uniformity, friability etc as per the method given by Indian Pharmacoepia and all the 18 formulations passed in these tests with values within the limit prescribed by the IP.

Floating Behaviour and Structural integrity

The floating lag time and total buoyancy studies were performed for the prepared tablets as per the method described previously in the methodology section. The lag time was found to be in the range of 8 to 31 seconds and all the formulations had a total buoyancy time of more than 12h. The floating lag time was found to be increases when the polymer concentration was increased. This was found to be true for both swellable polymer and the release retardant polymer. The structural integrity of all the formulations were maintained upto 12h except in formulations without Eudgragit S100. Overall carbopol containing formulations had better matrix integrity as compared to HPMC containing formulations.

***In Vitro* Drug Release Studies**

The *in vitro* drug release studies of all the formulations were studied using USP Type II Paddle apparatus with pH 1.2 acidic buffer as the dissolution medium. The study was performed for 12h and an average of three determinations was reported. From the observed results it was noted that the carbopol containing formulations had a more sustained release than the HPMC containing formulations which may be due to the high swelling capacity of carbopol. In both formulations, as the concentration of the swellable polymers were increased, a decrease in the drug release was observed. Likewise, as the concentration of Eudragit S100 was increased, the drug release was found to be decreased. Since Eudragit S100 is not soluble in acidic pH, it may reduce the permeability of the fluid inside the matrix and hence may have caused the reduction in drug release. Although all the formulations showed complete release, the time taken was found to be very short which is not suitable for sustained release effect. Formulation C8 with 90mg carbopol and 60mg Eudragit S100 and formulation H9 with 120mg HPMC and 60mg Eudragit S100 showed a better sustained effect with the complete release of the drug spreading over 12h and hence these two formulations were chosen as best formulations.

CONCLUSION

Gastro retentive dosage forms are gaining more importance in the field of drug delivery research especially for those drugs whose absorption and oral bioavailability can be improved when it is delivered in acidic conditions. In this study we have successfully developed oral floating tablets of Lamivudine with the use of polymers like carbopol, HPMC, and eudragitS100. The formulations showed excellent floating characteristics with good matrix integrity and sustained release of the drug spread over 12 hrs. Since the gastric residence time of the drug can be substantially increased by these types of sustained release formulations, it can be expected that drug will have complete absorption and improved bioavailability and also a reduction in the frequency of drug administration because of the sustained release effect. This may also decrease the stomach pain associated with repeated administration of conventional Lamivudine tablets. From this research work we have concluded that oral floating systems can be developed successfully using a combination of carbopol/HPMC and Eudragit S100 .Further studies using animal model will throw more light on the effectiveness of the formulation *in vivo*.

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