INTERNATIONAL JOURNAL OF PHARMACEUTICAL RESEARCH AND NOVEL SCIENCES

IJPRNS

DEVELOPMENT AND FORMULATION OF LAMIVUDINE MATRIX BASED CONTROL RELEASE TABLETS USING DIFFERENT CELLULOSE AND EUDRAGIT POLYMERS

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ABSTRACT
In the present study an attempt has been made to develop Lamivudine matrix tablets using Eudragit RLPO and RSPO. The matrix tablets were prepared by wet granulation method with different concentrations of Eudragit RLPO and RSPO and in combination with Ethyl cellulose. Preformulation study was done initially and results directed for the further course of formulation. Based on Preformulation studies different formulations of Lamivudine were prepared using selected excipients. All the Physico chemical parameters like hardness, friability and drug content have been evaluated. Results of the present study demonstrated that combination of both hydrophilic and hydrophobic polymers could be successfully employed for formulating controlled release matrix tablets of Lamivudine.

Key Words: Lamivudine, matrix tablets, Eudragit RLPO and RSPO

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INTRODUCTION

The development of controlled-release formulations continues to be a big success for the pharmaceutical industry. The success of any technology relies on the ease of its manufacturing process and its reproducibility of desirable biopharmaceutical properties. The technologies behind oral drug delivery have emerged from the mainstream pharmaceutical industry and have become influential forces in their own right, as evidenced by the upcoming "drug delivery companies" that are at the in front of innovation and hold their own niche market. Drug delivery systems are becoming increasingly sophisticated as pharmaceutical scientists acquire a better understanding of the physicochemical and biological parameters pertinent to their performance. For every disease or disorder state of the patient, proper medication is of prime importance to maintain

the patient in good health. To achieve this, the or more of several well defined and popular routes of drug administration including oral, parenteral, rectal, alveolar, and ocular, topical. Among these above mentioned popular routes, oral conventional route of drug administration lies at the top of the hierarchy of the conventional routes (1). High patient compliance and flexibility in developing dosage forms made the oral drug delivery systems the most convenient mode of drug administration compared to other dosage forms. In conventional oral dosage forms drug dosage must be taken several times which results in fluctuating drug levels in plasma. This drawback of conventional dosage form can be overcome by formulation of sustained release dosage forms which provides drug release in an amount sufficient to maintain the therapeutic drug level over extended period of time. The sustained release dosage form is defined as "any drug or dosage form modification that prolongs the therapeutic activity of the drug".Once the maximum level is reached, the amount of drug in the body decrease slowly so it will take longer time to drop below the therapeutic range.

The terms sustained or controlled drug release incorporates the element of prolongation of duration of action as well as the drug predictability and reproducibility in drug release kinetics (2).Polymeric sustained drug delivery systems is one which offers numerous advantages when compared with conventional dosage forms, including improved efficacy, reduced toxicity and improved patient compliance (3, 4).

Objective of the work is to develop A stable, pharmaceutically equivalent, and robust formulation of Lamivudine matrix controlled release formulation, which is an orally administered antiviral.

medicine drug is administered conventionally by one

MATERIALS AND METHODS

Materials

Lamivudine USP, Eudragit RLPO, Eudragit RSPO, Ethyl cellulose BP, Magnesium Stearate BP and Potassium dihydrogen Phosphate BP from Aurobindo Pharma Ltd., Hyderabad (Andhra Pradesh).

Methods

Formulation of Lamivudine Matrix Tablets Using Different Ratios of Polymers

Lamivudine matrix tablets were prepared by wet granulation technique with various ratios of Eudragit RLPO, Eudragit RSPO, and Ethyl cellulose as per the formula in Table-1.

Wet Granulation Method

The method for production of lamivudine controlled release tablets is wet granulation method (5). All ingredients was collected and weighed accurately. Sifted lamivudine USP with mannitol and polymers passed through sieve no 40#.Lamivudine was mixed with required quantity of polymers like eudragit, ethyl cellulose. Eudragit polymers are taken in the increasing ratios like 15 %, 30 %, 45 %, and 60 % w/w of the drug. Ethyl cellulose is taken 50 % to the weight of the polymer. povidone in isopropyl alcohol is used as binder. Lamivudine and polymer mixture is granulated using binder solution. The wet mass is passed through sieve #16 and dried at 55 ^{0}C ± 5 ^{0}C for 1 hour. After adequate drying the granules were passed through sieve #22. The granules were lubricated with magnesium stearate. The lubricated granules are compressed using beveled flat faced punches of 8 mm diameter. Parameters like average weight, hardness, friability are checked during compression as in process

Table-1 Formulation of Controlled Release matrix tablets of Lamivudine

Ingredients (mg)	**EL_1**	**EL_2**	**EL_3**	**EL_4**	**EL_5**	**ES_1**	**ES_2**	**ES_3**	**ES_4**	**ES_5**
Lamivudine	200	200	200	200	200	200	200	200	200	200
Eudragit RSPO	--	--	--	--	--	30	60	90	120	75
Eudragit RLPO	30	60	90	120	75	--	--	--	--	--
Mannitol	159	129	99	69	51	159	129	99	69	51
Povidone K 30	9	9	9	9	9	9	9	9	9	9
Ethyl Cellulose	--	--	--	--	60	--	--	--	--	60
Magnesium Sterate	2	2	2	2	5	2	2	2	2	5
Water	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs
Isopropyl alcohol	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs
Total weight	400	400	400	400	400	400	400	400	400	400

RESULTS AND DISCUSSION

Characterization of granules

The granules of matrix tablet were prepared and characterized. The angle of repose was less than 30 for all the batches of granules indicating satisfactory flow behavior. Moisture content of less than 3 % indicates optimum drying of granules. The compressibility index indicates the compressibility of the granules, which was found to be normal. The values of bulk density, tapped density, and compressibility index were given in Table -2.

Table-2 Characterization of Granules

Batch	**Angle Of repose (^{0})**	**Bulk density (g/cc)**	**True density (g/cc)**	**Carr's index (%)**	**Moisture content (%)**
EL_1	28	0.61	0.76	19.1	2.3
EL_2	24	0.57	0.67	18.7	2.4
EL_3	27	0.65	0.79	17.5	1.9
EL_4	28	0.42	0.62	20.3	2.5
EL_5	26	0.50	0.61	18.7	2.3
ES_1	24	0.54	0.70	19.4	2.1
ES_2	26	0.51	0.71	20.1	2.3
ES_3	25	0.46	0.67	18.2	2.3
ES_4	28	0.62	0.80	17.4	2.4
ES_5	27	0.56	0.67	17.9	2.6

Characterization of matrix tablets

The tablets of different formulations were subjected to various evaluation tests, such as weight variation, friability, hardness according to procedure specified in I.P. The
friability was less than 0.4 %. Drug content was more than 95 %. The results are given in Table-3

Table-3 Characterisation of Matrix Tablets of Lamivudine

Formulation code	Weight variation (mg)	Hardness (kg/cm^2)	Friability (%)	Content uniformity
EL_1	400	6.3	0.24	98.3
EL_2	401	6.2	0.32	98.1
EL_3	396	6.4	0.11	98.7
EL_4	395	5.9	0.22	98.7
EL_5	395	6.6	0.34	98.6
ES_1	398	6.5	0.11	99.4
ES_2	401	6.7	0.36	98.8
ES_3	399	6.3	0.29	99.2
ES_4	396	6.5	0.33	98.3
ES_5	397	6.4	0.32	98.3

In Vitro Drug release studies

Dissolution profiles of batches **EL_1, EL_2, EL_3** and **ES_1, ES_2, ES_3** are shown in Table-4. The batch **EL_1** which contains 15 % w/w Eudragit **RLPO** polymer to drug, released 97 % of the drug at the end of 4th hour. **EL_2** batch is prepared by increasing the polymer concentration from 15 % w/w of drug to 30 %w/w of drug. EL_2 was able to sustain the drug release up to 6 hours (96 %), so next batch **EL_3** is prepared by increasing the concentration of polymer to 45 % w/w of drug. EL_3 was able to sustain the drug release up to 8 hours (96 %). In the same way Eudragit **RSPO** formulations ES_1 sustained the drug up to 4 hours (99 %) when added at the concentration of 15 % w/w of drug, up to 6 hours (97 %) at 30 % w/w of drug and up to 8 hours at 45 % w/w (97 %) of drug. Further increase in concentration of polymer Eudragit RLPO, **EL_4** was able to sustain the drug release up to 10 hours (99%) at 60 % w/w of drug and Eudragit RSPO, **ES_4** 60 % w/w of drug (99 % at the end of 10 hours) did not significantly effect the release rate. On this basis EL_3 and ES_3 were selected for further studies. To these formulations, Ethyl cellulose 50 % w/w of polymer (**EL_5 and ES_5**) was added, and matrix tablets are formulated.

EL_3 and ES_3 batches have shown more than 50 % release at the end of 2.5 hours and more than 90 % drug release at the end of 8 hours but batches **EL_5 and ES_5** which are formulated with the addition of Ethyl cellulose 50 % w/w to Eudragit RLPO and RSPO polymers have sustained the release up to 4.5 hours for releasing 50 % of drug and up to 15 hours for releasing 90 % of the drug. This clearly reveals that addition of 50 % w/w Ethyl cellulose in batches EL_5 and ES_5 were sustaining the drug release up to 12 hours. So they can be considered as a once in a day dose for Lamivudine in matrix tablets. Release profile of all batches is represented in Fig-1.

Table -4 *In Vitro* Drug Release Profiless

Time (hrs)	Cumulative % drug release from RLPO&RSPO matrix tablets									
	EL_1	**EL_2**	**EL_3**	**EL_4**	**EL_5**	**ES_1**	**ES_2**	**ES_3**	**ES_4**	**ES_5**
1	53.48	36.45	29.33	31.23	15.54	54.12	40	32.14	31.42	16
2	81.34	57.34	45.77	45.57	30.63	83.84	59.59	46.67	43.26	29.37
3	90.67	68.34	56	57.23	41.67	93.50	72.34	60.33	58	37.33
4	96.49	78.37	66.12	68.24	51.33	98.33	80.19	70.64	67.23	46.43
5	-	84.85	76	75.4	55.45	-	87.54	76.54	74.82	52.22
6	-	96	81	83.34	60.12	-	96.2	81.39	82.59	58.35
7	-	-	86.49	88.25	65.06	-	-	89.63	87.73	62.64
8	-	-	95.78	93.65	70.19	-	-	96.30	93.34	68.19
10	-	-	-	99.5	80.49	-	-	-	99	74.49
12	-	-	-	-	85.46	-	-	-	-	81.86

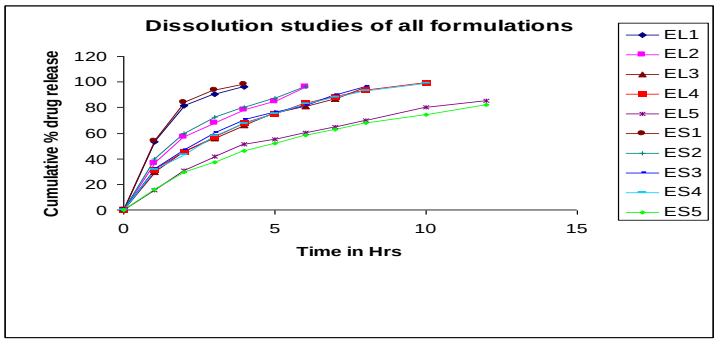

Fig -1 Comparative dissolution profile of all Formulations

CONCLUSION

Results of the present study demonstrated that combination of both hydrophilic and hydrophobic polymers could be successfully employed for formulating controlled release matrix tablets of Lamivudine. It can be concluded that the polymer plays a major role in the design of sustained release matrix tablet. The study reveals that the release of drug is low when the matrix tablet contained hydrophilic and hydrophobic polymers as a combination than the other matrices.

From the above results and discussion it is concluded that the matrix tablet formulated using Eudragit RSPO and combination with Ethyl cellulose had sustained the drug release better than the other batches.

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