ISSN: 2455-281X

Contents lists available at http://www.albertscience.com

ASIO Journal of Pharmaceutical & Herbal Medicines Research (ASIO-JPHMR)

Volume 5, Issue 1; 2019; 49-54

DESIGN AND DEVELOPMENT OF TASTE MASKED FORMULATIONS OF MODEL DRUG BY USING EUDRAGIT L -100

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ARTICLE INFO

Research Article History

Received: 25th May, 2019
Accepted: 20th July, 2019

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ABSTRACT

In the oral dosage form taste of a drug plays an important role in patient compliance, Tenofovir disoproxil fumarate is a nucleotide reverse transcriptase inhibitor drug with an extremely bitter taste. In the current research work, an attempt was made to mask the bitter taste of Tenofovir Disproxil Fumarate by complexation technique, with a formulation into oral dispersible tablets, using super disintegrant croscarmellose sodium in different concentration. Polymer Eudragit L -100 was used in the formulation of the complex with the Tenofovir Disproxil Fumarate. The complexes were formulated as 1:1, 1:2 and 1:3 ratios. The loading process was optimized by the drug and polymer ratio. The prepared complexes were analyzed for taste masking by panel method and characterized by FTIR. Using the optimized drug-polymer complexes (1:3 ratio), oral dispersible tablets were prepared and evaluated for pre-formulation and post formulation parameters. The formulations were subjected to thickness, hardness, diameter, weight variation test, friability test, disintegration time, in-vitro dissolution time and stability study. All the parameter passes the test. This finding can be utilized to formulate a non-bitter dosage form for Tenofovir Disoproxil Fumarate with good bioavailability and stability.

Keywords: Taste Masking, Complexation, Eudragit L -100, Oral Dispersible Tablets.

1. INTRODUCTION [1-3]

Drugs are most important part which has to be developed into a satisfactory dosage form. About 70 % preparation available in market are solid from composed of tablet, capsule and powder i.e. dry syrup, effervescent powder, powder for topical use, powder for injection etc. Oral route offers convenience and ease of administration, greater flexibility in dosage form design. These dosage forms are designed either for improving the physical and mechanical properties of materials during manufacturing. Oral administration of bitter drugs is important problem for health care providers especially with pediatrics and geriatric patient.

Extents of Bitter Taste, Dose of Active Pharmaceuticals, Drug Particle Shape and Size Distribution, Dosage Forms, Drug Solubility, Ionic Characteristics of the drug are the factor which affects selection of taste masking technology.

The concept of fast disintegrating drug delivery system emerged from the desire to provide patients with conventional means of taking their medication. Undesirable taste is one of the important formulation problems in oral dosage form. Taste of a pharmaceutical product is an important parameter for governing compliance.

MATERIALS AND METHODS:

Tenofovir Disoproxil Fumarate was obtained as a gift sample from Cipla Drug Pharmaceutical Ltd, Mumbai. Eudragit L-100 gets by Yarrow Chem Products, Nagpur. Other chemicals used were of analytical grade.

FTIR STUDY OF TENOFOVIR DISOPROXIL FUMARATE:

Drug exicipients interaction study was done by using the Fourier transform infrared spectroscopy (FTIR) spectroscopy of optimized batches. Fourier transform infrared (FTIR) spectroscopy was employed to characterize further the possible interaction between the drug and the carrier in the solid state on a FTIR spectrophotometer by the conventional KBr pellet method. The spectra were scanned over a frequency range 4000-400 cm^{-1}.

TASTE MASKING OF TENOFOVIR DISOPROXIL FUMARATE

Preparation of Drug and Eudragit L-100 Complex [4]

Taken Acetone required to disperse the accurately weighed quantity of polymer Eudragit L-100 in it. Stirred for few min and then added weighted quantity of drug, stirred for 10-15 min with 4000 rpm to ensure uniform dispersion of drug particles. Transferred the microcapsule in tray and allowed drying at room temperature for 24 hours to ensure complete evaporation of acetone. Complex were crushed and then passed through sieve # 80 to get the uniform, free flowing and discreet particles.

The complex were separately prepared using polymer Eudragit L-100 in Drug: Polymer ratio 1:1, 1:2 and 1:3 following the same procedure. Drug proportion was maintained constant so as to determine maximum polymer required to encapsulate drug, and to obtain desired drug release.

TASTE EVALUATION OF COMPLEXES

The taste of complexes was checked by panel method. For this purpose, 10 human volunteers were selected. About50 mg of drug equivalent complex was placed on tongue and taste evaluated after 10 s.

METHOD OF PREPARATION

Preparation of Tenofovir Disoproxil Fumarate Tablets

Direct Compression Technique:

In this method, all the powder excipients were mixed in a mortar pestle. After proper mixing, the powder was punched into tablets. The weight of the tablet was 425 mg and dose of the drug is 80 mg. The excipients were selected from the drug excipients compatibility study and used in the final formula within the limit of inactive ingredient guide available by FDA.

Table 1: Different formulation of Tenofovir Disoproxil Fumarate oral dispersible tablets.

Sr. No.	Name of Ingredients	Quantity in mg of components for 1 tablet		
		F1(mg)	F2(mg)	F3(mg)
1	Drug polymer complex (DRC)	320	320	320
2	Microcrystalline cellulose	30	30	30
3	Mannitol	20	20	20
4	Talc	10	10	10
5	Magnesium Stearate	5	5	5
6	Crosscarmellose	40	40	40
7	Acacia	_	22	_
8	Starch paste 3%	_	_	Q.S.
total		**425 mg**	**447 mg**	**425 mg**

PRE-COMPRESSION STUDIES OF POWDER BLENDS:

Various pre-compression parameters like Bulk Density, Tapped Density, Angle of Repose, Carr's Index, Hausner's ratio were performed.

POST-COMPRESSION STUDIES OF TENOFOVIR DISOPROXIL FUMARATE TABLETS

i. **Hardness Test**

Hardness of the tablet was determined using the Monsanto hardness tester. The force required to break the tablet is measured in kilograms.

ii. **Thickness Test**

The thickness of the tablet is mostly related to the tablet hardness can be uses as initial control parameter. Tablet thickness was determined using a Vernier caliper and the reading was recorded in millimeters.

DOI Link :: http://doi-ds.org/doilink/10.2016-19146535/ ; doi: http://doi-ds.org/doilink/08.2019-13718192/

Friability Test

Friability is measured by the use of the Roche friabilator. The pre-weighed tablets were placed in the friabilator which was then operated for 100 rpm, then dusted and reweighed.

Weight variation test

Ten tablets of each formulation were selected at random and weighed individually. The weight of individual tablets was noted. Average weight was calculated from the total weight of all tablets. The individual weights were compared with the average weight. Not more than two of the tablets must differ from the average weight.

Disintegration time study

The test was carried out on tablet using distilled water at 37^{0}C + 2^0 C was used as disintegration media and the time in second taken for complete disintegration of the tablet with no palatable mass remaining in the apparatus was measured in seconds.

Wetting time study

A piece of tissue paper folded twice was placed in a small Petri dish (internal diameter = 6.5cm) containing 5 ml of distilled water. A tablet was placed on the paper, and the time for complete wetting of the tablet was measured in seconds.

IN VITRO DRUG RELEASE STUDY

In vitro release studies were carried out by using USP paddle dissolution test apparatus. 900 ml HCl solution of pH 1.2 and phosphate buffers of pH 6.8 was taken in the dissolution vessel and the temperature of the medium was maintained at 37±0.5^{o}C. 50rpm was maintained, 0.5 ml of sample was withdrawn at predetermined time intervals for 15, 30 and 45 mints. The same volume of the fresh medium was replaced .The samples were analyzed at 261nm by using a UV spectrophotometer. The dissolution data obtained were plotted as percentage drug release versus time.

STABILITY STUDIES

Stability studies are used to find out whether any chemical degradation of tenofovir disoproxil fumarate formulations takes place or not. The formulated tablets were stored at 45^{0}c ± 2^o C temperature in accelerated stability chamber for 30 days. The tablets were taken from the stored samples after 30th days and analyzed for drug content and in vitro release studies were carried out to determine the percentage of tenofovir disoproxil fumarate released.

RESULTS AND DISCUSSIONS

FTIR STUDY OF TENOFOVIR DISOPROXIL FUMARATE

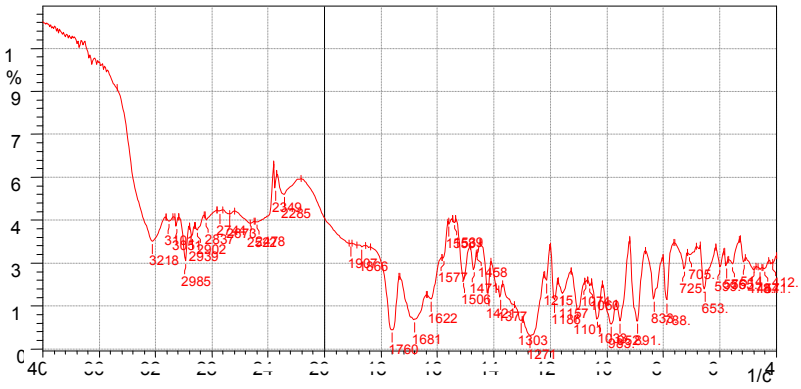

Fig. 1: Drug: Tenofovir Disoproxil Fumarate FTIR characterization.

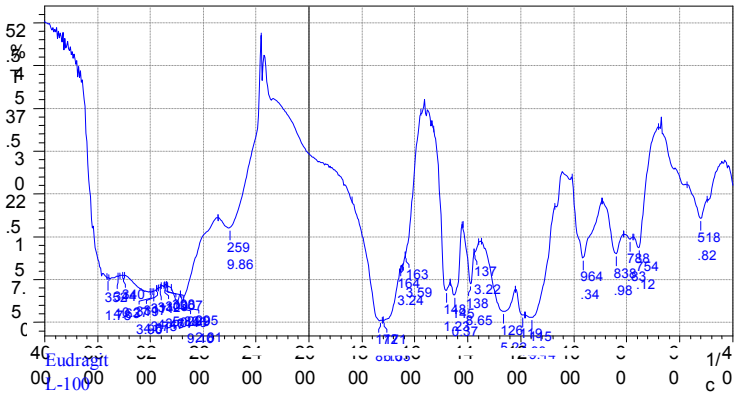

Fig. 2: FTIR spectra of Eudragit L- 100.

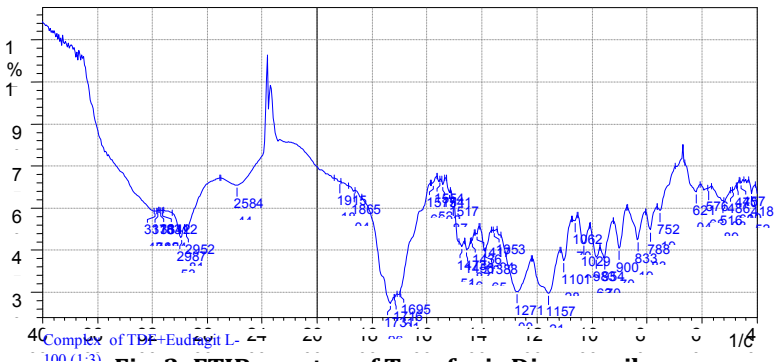

Fig. 3: FTIR spectra of Tenofovir Disoproxil Fumarate and Eudragit L 100 (1:3) complex

From the peak values of IR spectrum of Tenofovir Disoproxil Fumarate, Eudragit L 100,Tenofovir Disoproxil Fumarate and Eudragit L 100 Complex, it had been observed that carboxylic acid – OH peaks at 3521 cm^{-1} had disappeared in the IR spectrum of drug polymer complex. Similarly it had been observed that there is absence of NH_2 peak which is at 3218 cm^{-1}concluding that OH of carboxylic and functional group of Eudragit L-100 and NH_2 of Tenofovir Disoproxil Fumarate interact with each other forming amide. Showing–N-H peak at 3178 cm^{-1} and C=O peak at 1695 cm^{-1}.

TASTE MASKING OF TENOFOVIR DISOPROXIL FUMARATE

Table 2: Various Ratios of Tenofovir Disoproxil Fumarate and Polymer in complexes.

Drug / Polymer	Ratio of Tenofovir Disoproxil Fumarate and / Polymer in complexes (in mg)		
Tenofovir Disoproxil Fumarate	80		
Eudragit L-100	80	160	240

TASTE EVALUATION OF COMPLEXES

Table 3: Taste Evaluation of Complexes

Sr. No.	Technique	Ratio	Polymer	Taste
T1	Complexation	1:1	Eudragit L-100	Bitter
T2	Complexation	1:2	Eudragit L-100	Slightly Bitter
T3	Complexation	1:3	Eudragit L-100	Tasteless

From the various trials of drug and resin/ polymer complex ratios **Eudragit L-100 (1:3)** ratio shows successfully taste masking of drug and it used for further studies.

EVALUATION PARAMETER

The blends of different formulations were evaluated for bulk density, tapped density, angle of repose, Carr's index and Hausner's ratio. The results of bulk density and tapped density ranged from 0.52 to 0.54 g/cm^3 and 0.60 to 0.65g/cm^3. The result of Angle of repose ranged from 38.65^0 c to 39^0 c. The result of Carr's index ranged from 17% to 18%. The result of hausner's ratio ranged from 1.20 to 1.21 from this study of the micromeretics properties of powder blend indicated good flow properties and compressibility of powder blend.

All the formulated dispersible tablet showed thickness in the range of 6.4 to 6.6 mm, diameter ranged 10.6 to 10.7 mm, hardness in the range of 1-2 kg/ cm^3, friability in the range of 0.47% to 0.89%, disintegration time in the range of 20 to 70 sec, wetting time 12 to 37 sec and weight variation test passes in the limit. Thus all the physical parameters of all formulations were within IP limit.

IN-VITRO DRUG RELEASE STUDY

Tablets formulation was subjected for *in-vitro* release studies. The results are presented in Table 4.

Table 4: Cumulative % drug release of tablet in HCl solution of pH 1.2

Sr. No.	Time (min)	% of drug release (HCl solution of pH 1.2)
1	0	0.00 %
2	15	91.605%
3	30	94.399 **%**
4	45	100.033 %

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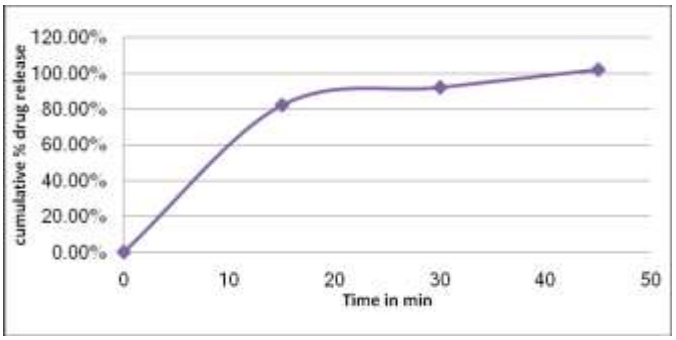

Fig. 4: dissolution of oral dispersible tablet of Tenofovir Disoproxil Fumarate in HCl solution at pH 1.2

Table 5: cumulative % drug release of tablet in phosphate buffer of pH 6.8

Sr. No.	Time (min)	% of drug release (phosphate buffer of pH 6.8)
1	0	0.00 %
2	15	86.078 %
3	30	96.049 %
4	45	102.254 %

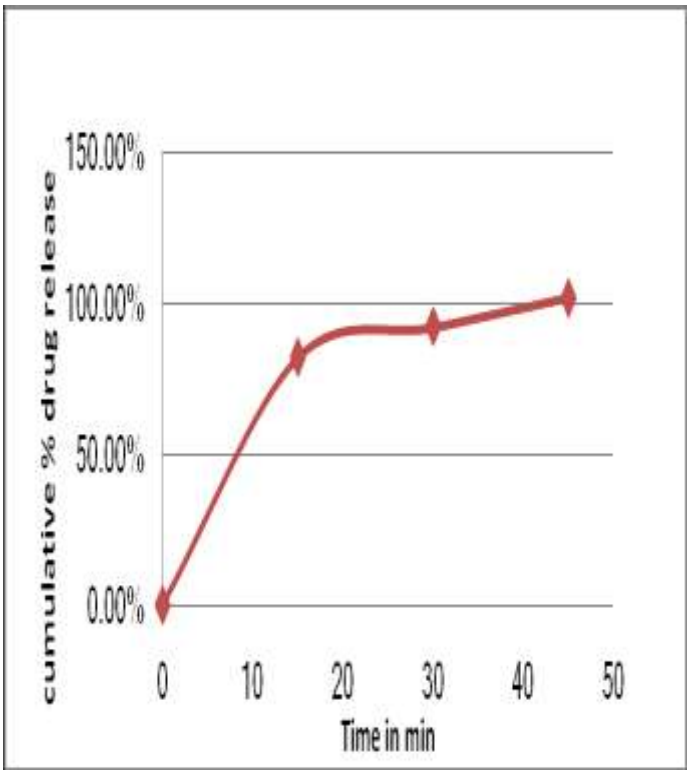

Fig. 5: dissolution of oral dispersible tablet of Tenofovir Disoproxil Fumarate in phosphate buffer pH 6.8.

STABILITY STUDIES

Table 6: drug release data of selected formulation before and after stability study

Formulation Code	Before stability studies			After 30 days of stability studies		
	Cumulative % drug release			Cumulative % drug release		
F3 Cumulative% of drug release in HCl solution at pH 1.2	**15 min**	**30 min**	**45 min**	**15 min**	**30 min**	**45 min**
	91.60%	94.39 **%**	100.03%	92.50%	95.60%	101.23%
F3 Cumulative% of drug release in Phosphate Buffer at pH 6.8	**15 min**	**30 min**	**45 min**	**15 min**	**30 min**	**45 min**
	86.07%	96.04 %	102.25 %	85.02%	98.04%	101.51%

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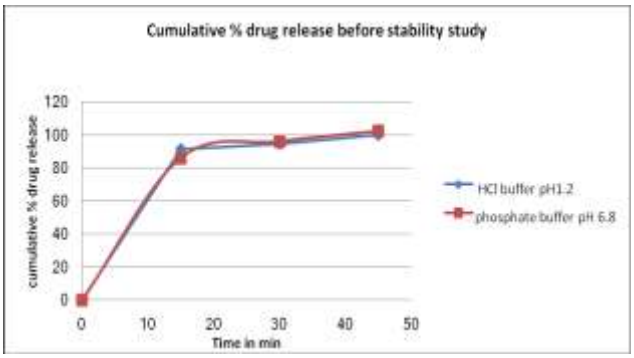

Fig. 6: Cumulative % drug release data before stability study

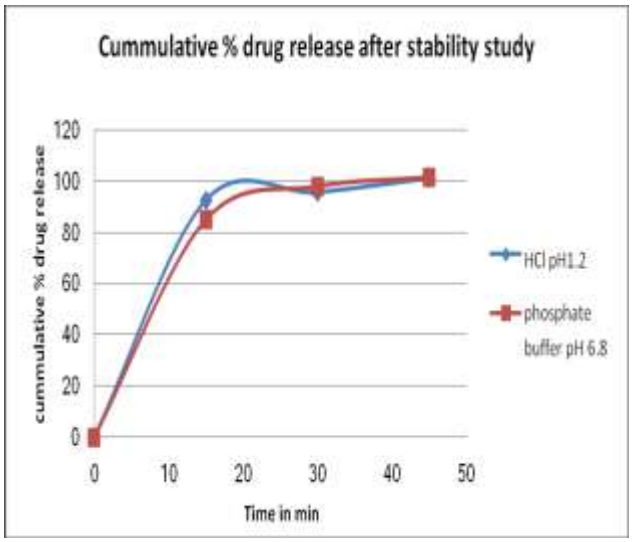

Fig. 7: Cumulative % drug release data after 30 days of stability study

Tenofovir disoproxil fumarate oral dispersible tablets formulations were stored in programmable environmental test chamber (45°C± 2°C) for 30 days.

At the end of 30 days of storage, the oral dispersible tablets were observed for changes in physical appearance analyzed for in vitro release studies.

There was no change in the percentage release of Tenofovir disoproxil fumarate from the formulations stored at different temperatures up to 30 days. Various Tablet evaluation tests were carried out like thickness, hardness, diameter, friability, weight variation disintegration time, wetting time there were no deviations in all the tests and all are within the limits. It showed that all the formulations are physically stable. There was no change in the formulation.

CONCLUSION:

Taste of Tenofovir disoproxil fumarate, a bitter drug, successfully masked by complexation with Eudragit L-100. The taste masked drug complex was used to prepare oro-dispersible tablets. The tablet formulated with cros carmellose sodium as super disintegrants. The studies of various formulation trials (F1-F3) were carried out with different concentrations of lubricants. From the various formulations it was concluded that the formulation batch of F3 was finalized as the optimized formula. Which (F3) showed satisfactory results with various physicochemical evaluation parameters like Disintegration time, Dissolution profile, and subjected to accelerated stability studies the Oral disintegrating tablets were found to be stable.

Acknowledgements:

The authors are grateful to the P. Wadhwani College of Pharmacy, Yavatmal. M.S. (45001), India for providing all the necessary facilities for carrying out the experimental studies.

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