DESIGN, DEVELOPMENT AND INVITRO EVALUATION OF BILAYER TABLETS OF LORATIDINE AND PHENYLEPHRINE

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ABSTRACT

The present study was carried out to develop the Bilayer tablets of Phenylephrine as sustained release and Loratidine as immediate release component. Phenylephrine is a selective α_1-adrenergic receptor agonist of the phenethylamine class used primarily as a decongestant, as an agent to dilate the pupil, and to increase blood pressure. Loratadine is a second-generation peripheral histamine H_1-receptor blocker used to treat allergies. In the present study the the bilayer tablets of Phenylephrine(SR) and Loratidine(IR) was formulated and evaluated, percentage friability for all the formulations was below1% indicating that the friability was within the range of standard specification. All the formulations showed post-compression parameters i.e friability and drug content were within acceptable official IP limits.Various sustained release formulations were formulated with super disintegrants, polymer alone; and microcrystalline cellulose was used as diluents. The tablets were evaluated for pharmacopoeial and non-pharmacopoeial (industry specified) tests. Based on the results, F-8, F-4 were identified as better formulation amongst all formulations.

KEYWORDS: Loratidine, Phenylephrine, Bilayer tablets.

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I. INTRODUCTION

Despite phenomenal advances in the inhalable, injectable, transdermal, nasal and other routes of administration, the unavoidable truth is that oral drug delivery remains well ahead of the pack as the preferred delivery route. There are of course many applications and large markets for non-oral products and the technologies that deliver them. However, if it is a viable option, oral drug delivery will be chosen in all but the most exceptional circumstances. These preparations are primarily intended to achieve faster onset of action for drugs such as analgesics, anmtipyretics and coronary vasodilators. Other advantages include enhanced oral bioavailability through transmucosal delivery and pregastric absorption, convenience in drug administration to elderly and bedridden and new business opportunities. Loratidine is a piperidine Histaminer H 1 receptor antagonist with anti allergic properties to relieve hay fever and allergic skin rash.[1-5] Phenylephrine is an alpha -1 adrenergic receptor used to treat hypotension and dilate the pupil to treat congestion nasal discomfort caused by colds and allergies.

II. MATERIALS AND METHODS

Table no 1. Showing materials with source and equipment

S.No	Name of Ingredients	Name of supplier	Name of the Equipment
1	Phenylephrine	Pharma remedics	Electronic balance
2	Loratidine	Reddy's lab	Bulk density apparatus
3	HPMC	Research-lab fine chem mumbai	Standard sieve (20 and 40#)
4	SSG	Research-lab fine chem Mumbai	Hot air oven
5	CCS	Virat Labs Hyderabad	Sixteen punch tablet compression machine
6	Crosspovidone	Research-lab fine chem Mumbai	Friability apparatus
7	Mg.stearate	Research-lab fine chem mumbai	Hardness tester
8	-	-	Varnier caliper
9	-	-	USP dissolution test apparatus Type II
10	-	-	UV spectrophotometer
11	-	-	FTIR spectrophotometer

Preparation of 0.1N hydrochloric acid:

0.1N HCl was prepared according to I.P. 1996. A quantity of 8.5 ml of HCl was diluted with fresh distilled water to produce 1000 ml.

Preparation of stock solution of Phenylephrine:

Accurately weighed 20 mg of Phenylephrine was dissolved in little quantity of distilled water and volume was adjusted to 100 ml with the same to prepare standard solution.

Procedure:

From the stock solution, aliquots of 1, 2, 3, 4, 5, 6, 7, 8 ml were transferred to 100 ml volumetric flasks and final volume was made to 100 ml with 0.01N HCl. Absorbance values of these solutions were measured against blank (0.01N HCl) at 205.5nm using Shimadzu-1700 UV spectrophotometer.[7-9]

Quantification of Drug

Accurately weighed 20 mg of Phenylephrine was dissolved in little quantity of distilled waterand volume was adjusted to 100 ml with the same to prepare standard solution. From the above solution, aliquots of 5 ml were transferred to 100 ml volumetric flasks and final volume was made to 100 ml with 0.01N HCl.[10-13] Absorbance values of these solutions were measured against blank (0.01N HCl) at 236nm using Shimadzu-1700 UV spectrophotometer.

Compatibility testing of drug with polymer

The proper design and formulation of a dosage form requires consideration of the physical, chemical and biological characteristics of all drug substances and excipients to be used in the fabricating the product. Each polymer used in the formulations was blended with the drug levels that are realistic with respect to the final dosage form. Each polymer was thoroughly blended with drug to increase drug- polymer molecular contacts to accelerate the reactions if possible.[13-17]

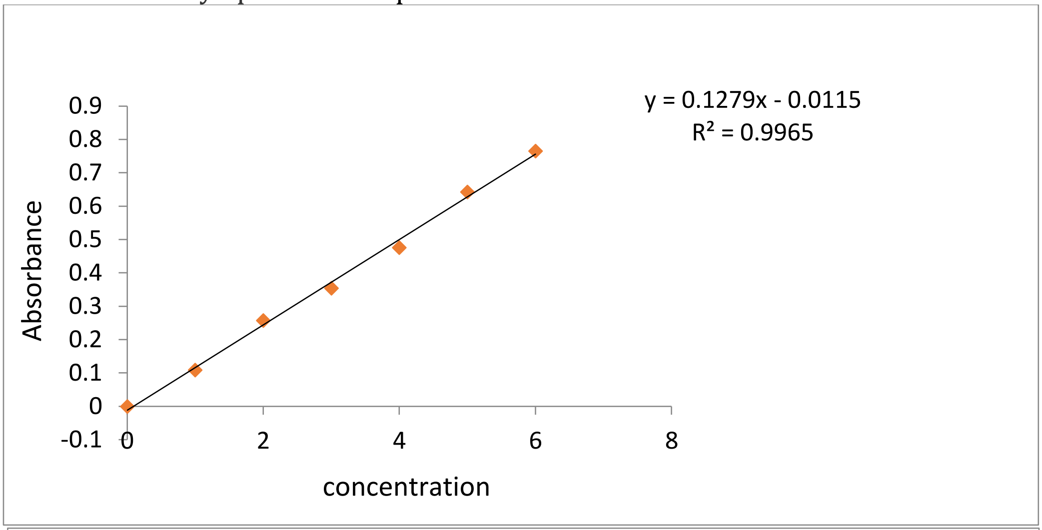
III. RESULTS AND DISCUSSION

Preparation of standard graph of Phenylephrine in 0.1N HCl.

UV absorption spectrum of Phenylephrine in 0.1N HCl shows λ max at 237nm. Absorbance values obtained for various concentrations of Phenylephrine in 0.1N HCl are given in table no 6.2. The graph of absorbance vs concentration for Phenylephrine was found to be linear in the concentration range of 2-16 µg /ml. The drug obeys Beer- Lambert's law in the range of 2-16 µg /ml was shown in Fig no 1

Preparation of standard graph of Phenylephrine in p^H 6.8 Phosphate buffer.

UV absorption spectrum of Phenylephrine in p^H 6.8 Phosphate buffer shows λ max at 238nm. Absorbances obtained for various concentrations of Phenylephrine in p^H 6.8 phosphate buffer are given in table no.6.3. The graph of absorbance vs concentration for Phenylephrine was found to be linear in the concentration range of 2-16 µg /ml. The drug obeys Beer- Lambert's law in the range of 2-16 µg /ml was shown in Fig no 1.



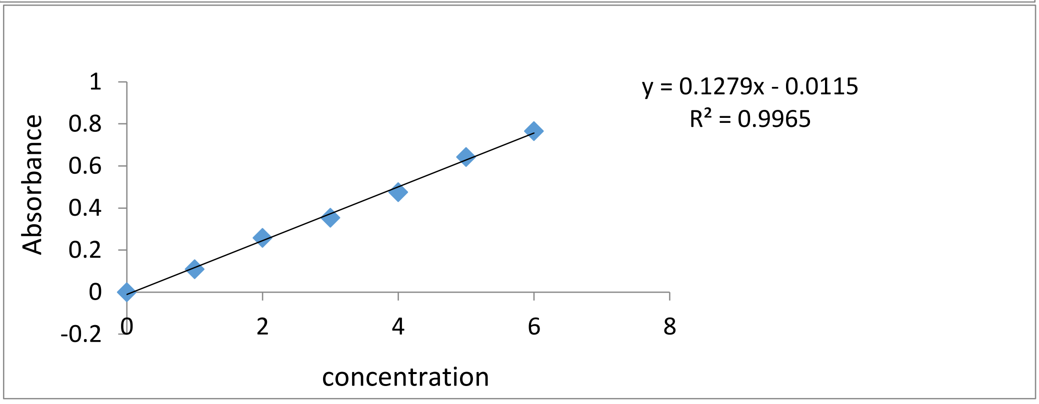


Fig-1: Standard graph of Phenylephrine and Loratidine of 0.1N HCl and pH 6.8 Phosphate buffer.

Bulk Density (BD)

The powder blends of formulations have the bulk density ranged between Sustained Release Formulations-0.439±0.0005 to 0.526±0.005 gm/ml. Immediate Release Formulations- 0.43 to 0.49gm/ml.

Tapped bulk density (TBD)

The powder blends of formulations have the tapped bulk density ranged between Sustained Release Formulations-0.867±0.0005 to 0.898±0.001 g/ml, Immediate Release Formulations-0.53-0.58. These values indicate good packing characteristics and the powder was not bulky.

Carr's Compressibility Index

The carr's index for all the both formulations was found to 12-18% indicating that the powders have a excellent compressibility.

Hausner's Ratio:

The hausner ratio for all the both formulations was found to be <1.25, indicating good flow.

Angle of repose:

The flow properties of granules were analyzed by determining angle of repose which was found to be between

Sustained Release Formulations- 20.07to 22.1,

Immediate Release Formulations-25.61-29.73. Excellent flow property.

Table 2. Physico-chemical characterization of Phenylephrine tablets and Loratidine

S.no	Formulation	Weight variation	Thickness	Hardness	Friability	Disintegration Time
1	F1	0.398	1.5	4	0.26	0.26
2	F2	0.415	1.6	4	0.62	0.62
3	F3	0.395	1.7	4.5	0.78	0.78
4	F4	0.413	1.6	4	0.79	0.79
5	F5	0.407	1.5	4.5	0.41	0.41
6	F6	0.386	1.6	4	0.38	0.38
7	F7	0.394	1.5	4	0.35	0.35
8	F8	0.405	1.6	4.5	0.36	0.36
9	F9	0.412	1.5	4.5	0.29	0.29

Invitro dissolution Studies of Phenylephrine and Loratidine :

Various sustained release formulations were formulated with HPMC K4M, K15M, K100M, polymer alone; and microcrystalline cellulose was used as diluents. The drug release data of dissolution studies of formulation f4 containing HPMC K100M is shown concentration levels were found to be 98.47% respectively was shown inn Table no 3.

Table 3. Dissolution data of formulations.

Time (hours)	Dissolution medium	% Drug release of F1	% Drug release of F2	% Drug release of F3	% Drug release of F4	% Drug release of F5	% Drug release of F6	% Drug release of F7	% Drug release of F8	% Drug release of F9
0	0.1 N HCl	0	0	0	**0**	0	0	0	0	0
0.5		12.43	5.16	3.16	**5.89**	13.46	5.12	3.79	8.56	13.49
1		21.65	13.46	9.19	**11.29**	25.54	11.25	9.46	18.64	23.76
1.5		30.21	2079	15.46	**24.57**	31.48	19.21	16.48	26.79	31.49
2		40.77	31.48	22.78	**31.87**	38.49	25.89	27.64	34.67	44.19
3	pH 6.8 phosphate buffer	46.10	46.19	29.16	**39.46**	45.76	36.19	35.57	44.59	50.73
4		54.69	59.87	38.46	**45.21**	57.49	45.73	43.58	57.19	64.18
5		65.87	67.46	44.59	**52.34**	66.87	56.79	56.78	64.28	74.46
6		75.63	78.46	50.76	**60.79**	79.47	62.49	69.47	79.49	88.46
7		83.61	88.76	60.46	**65.16**	88.87	70.23	75.89	88.46	99.91
8		95.89		65.16	**72.46**	100.78	79.45	85.46	99.76	
9		100.69		69.46	**80.77**		87.74	99.46		
10				72.46	**98.47**		98.16			

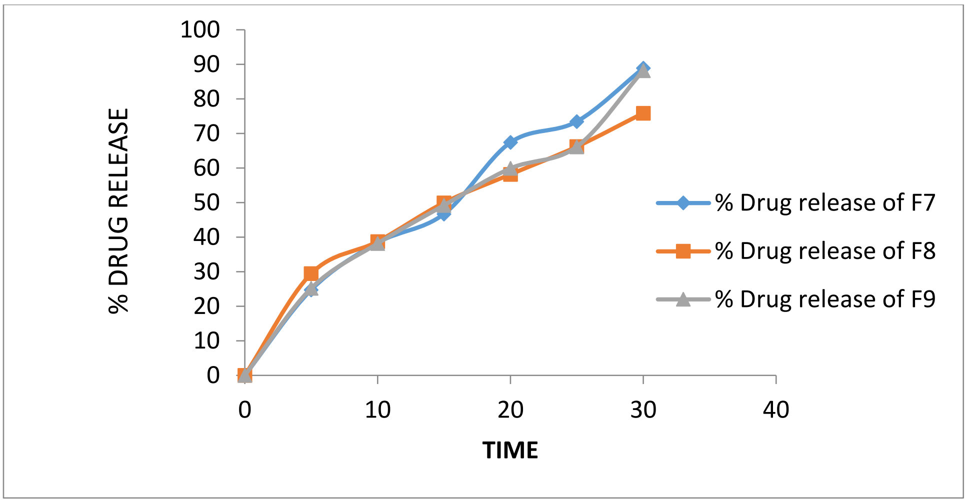


Fig-2: 20% drug release of formulation F7, F8, F9

Various sustained release formulations were formulated with super disintegrants, polymer alone; and microcrystalline cellulose was used as diluents. The drug release data of dissolution studies of formulation f4 containing is shown concentration levels were found to be 98.16% respectively

Summary

Oral route of administration is the most widely accepted route of delivery due to the ease of administration, avoidance of pain and other risks of parenteral administration and has good patient compliance.

The goal of any drug delivery system is to provide a therapeutic amount of drug to the target site in the body and also to achieve and maintain the desired plasma concentration of the drug for a particular period of time. The goals of sustained drug delivery are to conserve and maintain effective drug concentration, eliminate night time dosage, improve compliance and decrease side effects thus, optimizing drug therapy.

The current investigation deals with the formulation of tablets using with different polymers. Polymers used were different grades of HPMC, eudragit etc. FT-IR study is important to understand the interaction between the drug and polymers. The FT-IR spectrum of all the combinations containing drug and one or more polymer shows same or slight shift in peak values when compared with the characteristic peak values of the pure drug.

Thus, from the above inference it was concluded that there was no interaction between the drugs and used polymers From the Fig. It was observed that there were no changes in these main peaks of FT-IR spectra of mixture of drug and polymers, which show there were no interactions between drug and polymers. The drug and excipients were mixed and it is used for pre-compressional parameters i.e., angle of reposes 23.01, 27.54. These results indicate that powder formulations are exhibit good flow characteristics.

Evaluation of tablets:

In the present study the percentage friability for all the formulations was below1% indicating that the friability was within the range of standard specification. All the formulations showed post-compression parameters i.e friability and drug content were within acceptable official IP limits.

Dissolution study:

In-vitro drug release study for the prepared SR tablets were conducted for period of 10 hrs using a USP type-II (paddle) apparatus at $37^0 \pm 0.5^0$C and 75rpm speed. The dissolution studies were carried out in 6.8 pH phosphate buffer under sink condition. Every 1-hour interval samples of 5ml were withdrawn from dissolution medium and replaced with fresh medium to maintain the volume constant. The sample solution was analyzed at 206nm for Phenylephrine by a UV-spectrophotometer.

The *In Vitro* release of the Phenylephrine SR tablets which are prepared with Eudragit L100 polymers. Dissolution profile of formulations shown and the maximum release was found to be 97.47% at 10 hours.

The *in-vitro* release of the Loratidine IR tablets are prepared with ccs polymer. Dissolution profile of formulations shown and the maximum release was found to be 98.22% at 10 mins

Release kinetics:

The dissolution data were examined for models of zero order, Higuchi, Korsemeyer Peppas and Hixon crowell model. The best fit model for the formulation F8 was found to be Peppas model the R^2 value for the formulation is 0.961 respectively and the mechanism is Anomalous Release.

CONCLUSION

The conclusions drawn from the present investigation were given below:

Suitable analytical method based on UV-Visible spectrophotometer was developed for Phenylephrineλ_{max} of 228 nm, 206nm were identified in 0.1N HCl and pH 6.8 Phosphate buffer. The tablets were evaluated for pharmacopoeial and non-pharmacopoeial (industry specified) tests. Based on the results, F-8, F-4 were identified as better formulation amongst all formulations. *In vitro* release profiles of optimized formulations of Phenylephrine F8 Formulation. The conclusions arrived in this thesis indicated that the formulations of Phenylephrine sustained tablets in this investigation was found to be satisfactory based on *in vitro* release studies. Thus the objectives envisaged in this thesis were arrived. The bioavailability of the drug can also be improved with this sustained drug delivery system which increase efficacy, compliance and better clinical usefulness of patients.

Conflict of interest

Not applicable

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