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RESEARCH ARTICLE

Stability Studies of Optimized Formulation of Losartan and Hydrochlorothiazide Bilayer Floating Tablets

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ABSTRACT

The prasent study was to develop an optimal gastroretentive drug delivery system for administering Losartan and Hydrochlorothiazide as a fixed dose combination for antihypertensive therapy**.** The bilayer tablets were prepared by direct compression method. Losartan potassium and Hydrochlorothiazide were formulated and optimized separately as a floating and immediate release layer. Losartan was formulated as a floating layer using hydrophillic swellable polymer HPMC K4M, ethyl cellulose (4cps) as a bouyancy enhancer and sodium bicarbonate as a gas generating agent. The amount of polymer blends was optimized using 2^3 full factorial design. The influence of experimental factors such as swelling agent concentration, buoyancy enhancer and gas generating agent on floating lag time, total floating time, T 50% and % drug release were investigated to get optimized formulation. The responses were analyzed using ANOVA and polynomial equation was generated for each response using MLRA. All formulations floated for more than 12 hours. The study revealed that the optimized bilayer floating tablet retains in rabbit stomach for 9 h. The optimized formulation was subjected to stability study for three months at 40^0C /75% RH. The stability study showed no significant change in appearance of tablets, floating characteristics, drug content and *in- vitro* drug dissolution.

Keywords: Bi-layer floating tablets, Optimization, ANOVA, Superdisintegrants, Release-retarding polymers, in vivo x ray imaging study.

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CONTENTS

1. Introduction

The word 'optimize' is defined as, to make as perfect, effective or functional as possible and optimization may be interpreted as the way to find those values of the dependent variable. The application of formulation optimization techniques is relatively new to practice of the pharmacy, when used intelligently, with common sense, these "statistical" methods will broaden the perspective of the formulation process. Before any experiment is conducted at the pre-formulation stage, certain problems arise. It is often known beforehand which variables will significantly influence the response(s). Using screening designs and ANOVA can solve the problem.

Optimization Process

- Effect of a factor on a response i.e., change in dissolution rate as the drug to polymer ratio changes.
- The relationship between various factors and response i.e., quantitative change of a response as we change the factors and its levels.
- The contributional effect i.e., whether two factors are contributing additively or antagonistically for a response. E.g., any relationship between lubricant concentration and glidant concentration on hardness of the tablet or flow property of the granules.
- The best formulation (according to our need).

In general the optimization process involves the following steps:

- Based on the previous knowledge or experience or from literature, the independent variables are determined or set in the beginning.
- Selection of a model based on the results of the factor screening.
- The experiments are designed and are conducted.
- The responses are analyzed by ANOVA, test on lack of fit, to get an empirical mathematical model for each individual response.
- The responses are screened by using multiple criteria to get the values of independent variables. For example restriction of hardness to 6-8 kg/cm² and disintegration time < 5 min for a tablet formulation to get the most probable values of the independent variables like lubricant type or its concentration, disintegrating agent, etc.

2. Materials and Methods

Preparation of controlled release floating tablets of Losartan Potassium: Tablets containing 50 mg Losartan potassium were prepared, according to the design depicted in Table 10, by direct compression. The respective powders, namely Losartan potassium, release-retarding polymer HPMC K4M, bouyancy enhancer ethyl cellulose (4cps)andgas generating agent NaHCO3 were passed through sieve no. 60, separately. Mixing of powders was carried out using a pestle and mortar for 10 min. Colloidal silicon dioxide and magnesium stearate were then added to the mixed powders. Mixing was continued for another 3 min. Finally, 300 mg of each mixture wereweighed and fed manually into the die of a 10 station rotary tablet machine (Rimek Mini Press-I), equipped with flat-faced punches (9.5 mm), to produce the desired tablets. The hardness of the tablets were adjusted at 5 kg/cm2 using a Monsanto hardness tester (Secor India).

Formulation of bilayer floating tablets:

Optimized formulation from immediate release layer and controlled release layer was used to formulate bi-layer floating tablet of Losartan potassium and Hydrochlorothiazide. Accurately weighted 50mg of immediate release layer powder blend and300 mg of controlled release floating layer powder blend individually. Batches of bilayer tablets were prepared by direct compression method according to formula given in Table 51. Initially controlled release powder blend fed manually into the dies of 10stations rotary tablet machine (Rimek minipress-1) and then compressed at low compression force to formed uniform layer of powder. Subsequently immediate release layer's powder blend of Hydrochlorothiazide was added overpre-compressed immediate release layer then increased compression force then compressed on 10 stations Rimek minipress-1tabletmachine by using 9.5 mm flat faced punch.

Accelerated stability studies of the optimized formulation: Stability of a pharmaceutical preparation can be defined as "the capability of a particular formulation in a specific container/closure system to remain within its physical, chemical, microbiological, therapeutic and toxicological specifications throughout its shelf life. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under influence of a variety of environmental factors such as temperature, humidity and light, and enables recommended storage conditions, re-test periods and shelf-lives to be established.

ICH specifications for stability study:

- Long term testing: $25^0C \pm 2^0C$ /60% RH ± 5% RH for 12 months.
- Accelerated testing: $40^0C \pm 2^0C$ /75% RH ± 5% RH for 6 months.

Procedure:

In the present study, accelerated stability studies of the optimized formulation was carried out as per the ICH guidelines, at 40 ± 2^0C/ 75±5% RH by using Thermo lab TH 90S stability chamber for 3 months. The samples were observed for drug content and *in vitro* release profile. For stability study, the tablets were sealed in aluminum packaging coated inside with polyethylene. These sample containers were placed in stability chamber maintained at 75% RH and 45^0c.

Evaluation of samples:

The samples were analyzed for the following parameters:

Physical evaluation:

Appearance: The samples were checked for any change in colour at every week.

Hardness: The samples were tested for hardness at every week.

Chemical evaluation:

Drug content: The samples were checked for drug content.
Floating behavior: The samples were checked for FLT and Total floating time.
Drug release: The samples were subjected to drug release studies.
Accelerated stability studies of the optimized formulation: Stability of a pharmaceutical preparation can be defined as "the capability of a particular formulation in a specific container/closure system to remain within its physical, chemical, microbiological, therapeutic and toxicological specifications throughout its shelf life. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under influence of a variety of environmental factors such as temperature, humidity and light, and enables recommended storage conditions, re-test periods and shelf-lives to be established.
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3. Results and Discussion

Optimized Formulation:
Based on the results obtained for Q12, FLT and T50%, batch F4 was selected as best batch. It was arbitrarily decided to select a batch of tablets that gives moderate floating behavior and drug release in a control manner. Batch F4 exactly fit in the criteria for drug release. (More than 95% drug release within 12hrs. The final selection is done after considering some aspects such as T50% and FLT. By fixing the desired response values in numerical optimization using Design expert software v 8.0.6.1 (STAT-EASE) the optimized formulation was formulated.

Table 1: Results of floating property of the Losartan floating tablets.

Formulation code	Floating lag time (sec)	Total floating time (hr)	% Swelling Index	T 50% (Hour)
F1	30.32 ±0.8	>12	46.57± 0.012	6.214
F2	58.25 ±0.9	>12	63.1 ± 0.018	9.286
F3	13.64±0.5	>12	59.52 ± 0.014	4.315
F4	20.15±0.4	>12	63.54 ± 0.021	4.169
F5	48.31±0.5	>12	79.13 ± 0.0135	7.296
F6	66.39±0.4	>12	67.21 ± 0. 04	7.539
F7	23.54±0.6	>12	50.59 ± 0.036	7.124
F8	56.81±0.5	>12	74.92 ± 0.0163	7.164
C1	49.26±0.4	>12	62.85 ± 0.0132	6.638

Table 2: Constraints for optimized formulation

Name	Goal	Lower limit	Upper limit
HPMC K4M	In range	20%	30%
NaHCO3	In range	10%	15%
Ethyl cellulose	In range	5%	10%
% CDR 12h	Maximize	64.335	95.46%
FLT	Minimize	13.64	66.39
T 50%	In range	4.169	9.286

Table 3: Comparision of observed value and predicted value for optimized formulation F4

Responses	Predicted value	Observed value	% deviation
Q12	95.001	95.46	0.459
FLT	21.2115	20.15	0.0615
T50%	4.266	4.169	0.097

Table 4: Evaluation data for optimized formulation F4

Parameters	Result
Thickness (mm)	3.941± 0.023
Hardness (kg/cm^2)	5.6±0.1
Friability (%)	0.152

Average weight variation	0.304±0.013
Drug content (%)	99.63
%CDR at 12h (Q12)	95.46%
Floating lag time (Sec)	20.15±0.4
T 50 %	4.169 h
Total floating time (h)	>12h

Table 5: Results of floating property of the Losartan floating tablets

Formulation code	Floating lag time (sec)	Total floating time (hr)	% Swelling Index	T 50% (Hour)
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F8	56.81±0.5	>12	74.92 ± 0.0163	7.164
C1	49.26±0.4	>12	62.85 ± 0.0132	6.638

Table 6: Results for stability studies of optimized formulation

Time (Month)	Evaluation parameters						
	Hardness (kg/cm^2)	Drug content (%)		Floating behavior		CDR (%)	
		LSP	HCT	FLT (sec)	TFT(h)	LSP	HCT
0	5.4	98.23	99.48	24.26	> 12	97.32	98.56
1	5.3	97.76	99.12	26.34	> 12	97.13	98.23
2	5.3	97.29	98.86	27.23	> 12	96.96	98.16
3	5.2	97.25	98.49	28.68	> 12	96.84	98.09

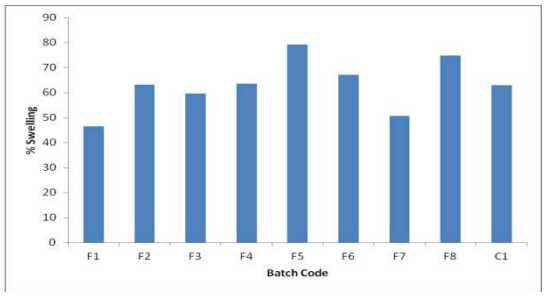

Figure 1: Swelling Index of factorial batches

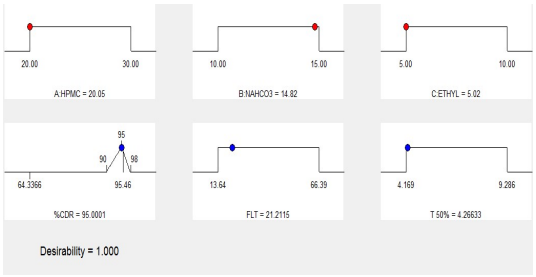

Figure 2: Numerical optimization Solution Tool Ramps

- HPMC K4M = 20.05% w/w
- NaHCO3 = 14.82% w/w
- Ethyl cellulose = 5.02% w/w
- MCC (PH102) = Q.S
- Magnesium stearate = 2%w/w
- Colloidal silicon dioxide = 0.5%w/w

The above concentration of ingredients was almost same as the value of factorial batch F4 formulation. Thus batch F4 was considered as the optimized batch.

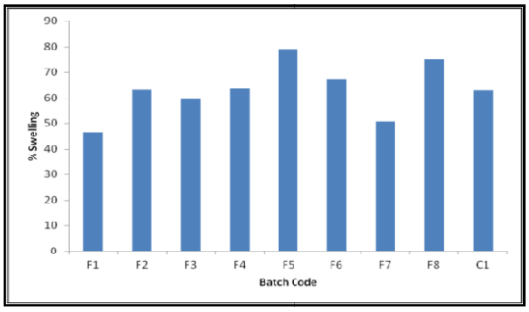

Figure 3: Swelling Index of factorial batches

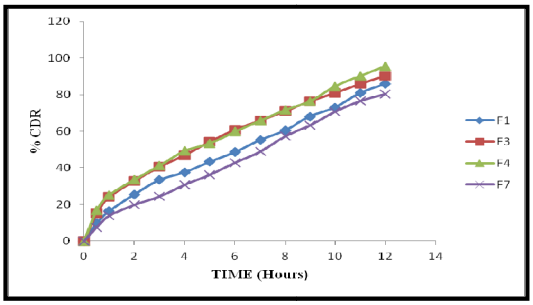

Figure 4: *In-vitro* cumulative percent drug release versus time for formulations F1, F3, F4 and F7

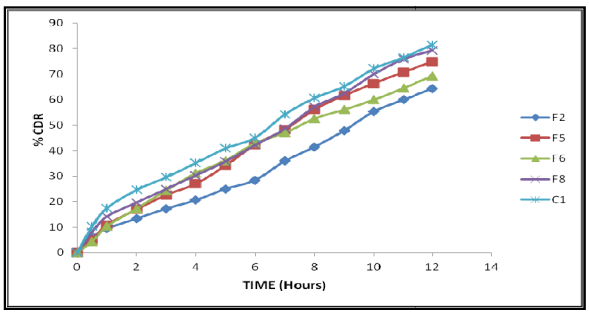

Figure 5: *In vitro* cumulative percent drug release versus time for formulations F2, F5, F6, F8 and C1

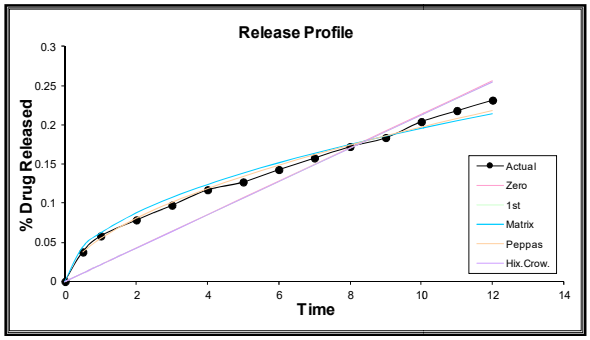

Figure 6: Drug release behavior of optimized formulation F4 with model fittings

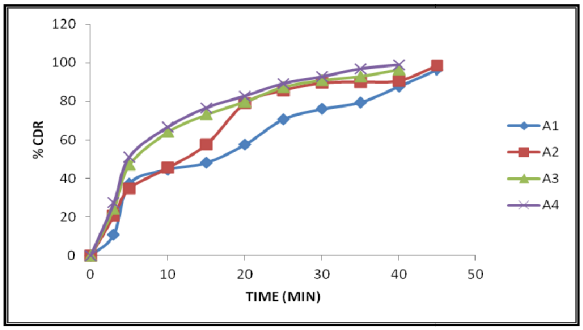

Figure 7: *In vitro* cumulative percent drug release verses time for formulation A1-A4

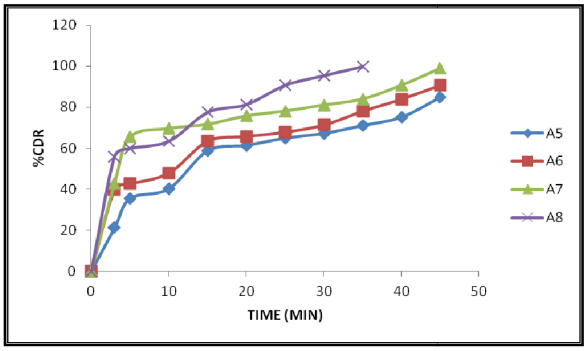

Figure 8: *In vitro* cumulative percent drug release verses time for formulation A5-A

Discussion

Multiple linear regression analysis was performed for dependent variables Q12, FLT and T50%. Polynomial equations and response surface plots were generated for all dependent variables. The factors selected were HPMC K4M, Sodium bicarbonate and Ethyl cellulose (4cps). From the ANOVA analysis it was found that all the three independent variables are significant for Q12 and FLT and for T50% HPMC K4M and NaHCO3 are significant.

Q12 =102.6103 - 1.60248X1 + 1.99615X2 - 1.00745X3

FLT = - 13.175 + 3.55275X1 - 1.9795X2 - 1.4965X3

T 50 % = 4.24025 + 0.234825X1– 0.36445X2 + 0.14325X3

In this linear model equation, the positive sign of coefficient indicates a synergistic effect while a negative term indicates an antagonistic effect upon the response. The largest coefficient means the causal factor has more potent influence on the response. From the result of multiple linear regression analysis it can be concluded that drug release pattern can be changed by appropriate selection of X1(HPMC K4M), X2 (Sod.bicarbonate) and X3(ethyl cellulose). Also the predicted values of responses for extra check point formulation C1 determined by putting the values of independent variables in the above generated polynomial equations was in close agreement with the observed values. Thus, we can conclude that the statistical model is mathematically valid.

Kinetic analysis of dissolution data:

The curve fitting results of the release rate profiles for the designed formulations were subjected for data analysis using PCP-V_2 dissolution software. It was found that all the formulations were fitted into Korsemeyers-Peppas model which is the best fitted model. From the Korsemeyers-peppas equation $t_{1/2}$ diffusion coefficient (n) and release rate constant (k) were calculated. These results confirmed that, the release mechanism for Losartan potassium floating tablets was by diffusion and swelling controlled mechanism i.e Non-fickian/anamolous transport where n value lies between 0.45 to 0.89 for all formulations. From the 'n' value of optimized formulation (0.5600) obtained it can said that the diffusion followed Non fickian mechanism and from regression coefficient value (0.9851) it can be said that it follows Peppas model for drug release.

For floating bilayer tablets:

Physicochemical characterization of bilayer tablets: The average weight (n=20), thickness (n=5) and hardness (n=5) of prepared tablet were found to be 348±2.03, 4.62 mm±0.055 and 5.4±0.2 kg/cm^2 respectively. The drug content of the prepared bilayer tablets (n=3) was found to be 98.23±1% (Losartan) and 99.48± 1.21% (Hydrochlorothiazide).

***In-vitro* drug release profile:**

The drug release profile of bilayer tablet was almost same as that of the optimized immediate release A8 formulation and controlled release floating F4 optimized formulation. More than 99% Hydrochlorothiazide released within 35 minutes where as Losartan releases in a sequential manner up to 12 hours as shown in Graph 31.

***In-vivo* mean gastric retention period:**

The data obtained from X-rays of the rabbit shows that the tablet reside in the stomach for 9hrs. (Figure 13)

Stability Studies:

Short term stability study was performed for optimized floating bilayer tablet formulation at 40±1^{0}C and RH 75% for 3 months (90 days). The samples were analyzed for percent drug content, *in-vitro* floating ability and *in-vitro*

drug release studies. The results are given in Table No 53. No appreciable difference was observed for the above parameters.

4. Conclusion

The floating, immediate and bilayer tablets were compressed using 9.5 mm, 4mm, 9.5mm circular flat faced punches using RIMEK I multi station rotary punching machine. Direct compression method was employed to formulate the tablets, because of its cost effectiveness and due to reduce number of manufacturing steps. The prepared floating tablet, immediate release tablet and bilayer tablets were evaluated for hardness, weight variation, thickness, friability, drug content uniformity, *in vitro* disintegration time, buoyancy lag time, total floating time, water uptake (swelling index), *in-vitro* dissolution studies. All formulations were subjected for five different models viz. Zero order, First order, Higuchi matrix, Peppas model and Hixson-Crowell equations and all the formulations followed Peppas model. Based on various evaluation parameters formulation F4 and A8 was selected as composition for bilayer floating tablet and was further subjected for *in vitro* release study, *in vivo* mean gastric retention period and stability study. *In vivo* mean gastric retention period revealed that the tablet remains inside the rabbits stomach for 9hrs±30 min. The optimized bilayer floating tablet showed good stability and values were within permissible limits. Thus conclusion can be made that stable floating dosage form can be developed for Losartan potassium and Hydrochlorothiazide for the controlled release bilayered floating tablets.

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