FORMULATION AND EVALUATION OF FLOATING TABLETS OF CAPTOPRIL UTILIZING OPTIMIZATION TECHNIQUE

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ABSTRACT

Floating tablets of Captopril were formulated utilizing optimization technique. Experimental design is a statistical design that prescribes a set of combination variables. Factorial design was chosen. A two level two factorial design was considered an ideal model to predict the effects of various factors like drug to polymer ratio, polymer to polymer ratio on the responses like buoyancy, $T_{0.5}$ and diffusion coefficient. In the present experiment Design 6.01 version was used to arrive at the polynomial equations for optimization method. The tablets were prepared by wet granulation method using HPMC, SCMC, MC as polymers. The tablets were evaluated for buoyancy, $T_{0.5}$ and diffusion coefficient. The formulations were subjected to stability studies (Deshpande, 1996).

1.INTRODUCTION

The word optimize is defined as to make things perfect, effective or functional as possible. Optimization may be interpreted as to find out the values of controllable variables that give the most desired value of the dependent variable. Optimization of pharmaceutical formulation with regard to one or more attributes has always been a subject of importance and attention for those engaged in formulations (Section3).

2. MATERIALS AND METHODS

Captopril was obtained as a gift sample from wockhardt Ltd, and Lupin Laboratories Ltd. The excipients were obtained from BPRL Ltd., Bangalore. Analytical grade chemicals and reagents were used.

Preparation of Floating Tablets of Captopril

The formulae for the formulation were arrived by utilizing optimization technique based on table 1 . A two level full factorial design was chosen as a good model to predict the effects of various factors like drug to polymer ratio, polymer to polymer ratio on responses like buoyancy, $T_{0.5}$ and diffusion coefficient .

FACTOR A: Drug to total Polymer content ratio (1:5 to 1:7)

FACTOR B: HPMC to Na CMC ratio (1:4 to 1:8)

The two level full factorial designs were considered with 2^2 factors. Totally 4 experiments have to be conducted. In order to see curvature effect, centre points are added. The total runs (experiments) will be 5. The runs formulated based on 2^2 factorial design were estimated drug content, evaluated for response parameters like duration of buoyancy, release profile and diffusion coefficient. From the data obtained by the runs, optimized formulae were arrived by using curve filling analysis in design expert 6.01 version software. Tablets were formulated by direct compression method in minipress tablet machine.

The actual quantities for the tablets are as per table1.

Parameters fixed for the tablets

1.	Tablet weight	-	250mg ± 18.6mg
2.	Thickness	-	4.5mm ± 0.5mm
3.	Hardness	-	3.5 ± 0.5kg / Cm^2
4.	Friability	-	Not more than 1%

Post Compression Parameters : The compressed tablets were evaluated for the parameters as shown in table2.

Evaluation: Estimation of captopril: The tablets were selected in random and average weight was calculated. The tablets were triturated to get fine powder; from the resulting triturate a weight equivalent to 25mg of the drug was taken. The triturate was grind to paste with small amount of gastric fluid. This mixture was suitably diluted, to get desired concentration range. The drug was estimated using Folin ciacalteau's reagent by colorimetric method at 760nm against reagent blank (Emmanuel, 1989).

Formula used:

$$\frac{\text{Sample abs}}{\text{Slope}} \times \text{dilution factor} \times \frac{25}{5} \times \text{Avg.wt of tablet}$$

Trial 1	Trial 2	Trial 3	Avg± SD
30.5mg	29.9mg	3o.5	30.3± 0.36

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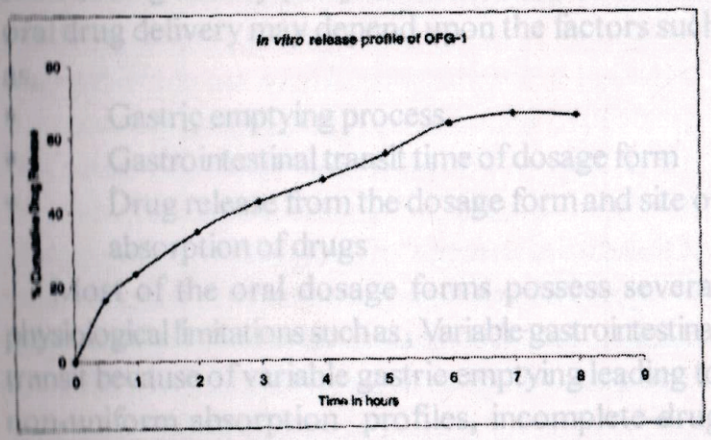
Response Evaluation

(a) In Vitro Release Profile : The dissolution was conducted as per the method reported by A.K. Hilten and PB Deasey. The dissolution media taken was 750ml of gastric fluid without enzyme maintained at 37^0 C. The paddle rotated at 50 rpm. About 5ml of media withdrawn and analyzed by colorimetric method using Folin's reagent at 760 nm against reagent blank [Table3].

(b) Duration of buoyancy: Duration of buoyancy was observed simultaneously when dissolution was carried out. The time taken by the tablet to rise to the surface of the media and the time for it to sink to the bottom was noted, which gives the buoyancy of the tablet (Menon and Ritchel,1994) [Table 3].



Statistical analysis:

The data obtained are subjected for curve fitting analysis. The results of curve fitting analysis are as recorded in the table.

Model	K	N	T0.5	R
Peppas	22.38h aff	0.5025	4.9515	0.996445
Higuchi	22.492	-	-	0.99644

I x swelling polymers and drug is

K – Release rate constant, N – Diffusion coefficient,

R – Regression coefficient.

Study of volume of tablet as a function of time

The process of drug release from a matrix swelling polymers and drug is a complex. The overall drug release is affected by the rate of water uptake and the diffusion rate of the drug through the swollen gel. The water uptake rate is enhanced in the presence of polymers with high hydrophilicity. Since sodium CMC has high affinity towards water this study would be relevant.

The thickness of gel layer formed varies with function of time. The gel increases the path length. If the plot between the square root of time and volume is linear, it indicates that the swelling process is dependent on the surface area exposed to the aqueous medium.

3.RESULTS AND DISCUSSIONS

Optimized formulae were arrived using the data obtained from the trial runs. Optimized formulations were prepared and evaluated. The predicted values in the optimized formula and the actual values of the responses obtained are as recorded in the table.

Responses	Predicted	Actual
T0.5 (hrs)	4.00	4.9515
Diffusion coefficient	0.4572	0.5025

The results indicate that there is less deviation of the actual values from the predicted values. Hence the model chosen for the optimization holds good for the experiment and serves the purpose desired.

Table No.1: The actual quantities of the formulation variables for the OFH-2

Sl No.	Ingredients	Quantity/ tablet (mg)	Quantity/ tablet (gm)
1	Captopril	30	3.000
2	Hydroxy propyl Methyl cellulose 4K	135.44	13.544
3	Sodium carboxy methyl cellulose HVP	16.93	1.693
4	Microcrystalline cellulose PH 102	62.63	6.263
5	Aerosil	1.25	0.125
6	Magnesium stearate	3.75	0.375
7	**Total**	**250**	**2.5**

Table No.2: Physical evaluation of OFH-2

Sl No.	Parameter	Inference
1	Tablet weight * (mg)	244.35 ± 4.295
2	Appearance	White, surface smooth and elegant in nature
3	Diameter (mm)	9.00
4	Thickness (mm)	4.7 ± 0.158
5	Hardness$^+$ (Kg/cm^2)	3.5 ± SD
6	Friablility$^+$(%)	0.229 ± 0.085
7	Assay$^+$ (mg)	30.30 ± 0.3464
8	Buoyancy$^+$ (Hours)	More than 12 hours
9	$T_{0.5}$ (Hours)$^+$	4.9515

* Average of 20 tablets, $^+$Average of three trials

Table 3

Time in Hours	Absorbance	Conc. in meg/ml	Conc. in 25ml (mg)	Conc. in 750ml (mg)	Cum. Loss to be added (mg)	Cum. Drug Release (mg)	% Cum. Drug Release ± SD
0.5	0.031	1.3305	0.0333	4.9893	0	4.9893	16.47±1.062
1	0.038	1.6309	0.0408	6.1159	0.0333	6.1491	20.29±0.524
2	0.053	2.2747	0.0569	8.5300	0.0740	8.6041	28.40±1.059
3	0.073	3.1330	0.0783	11.7489	0.1309	11.8798	39.21±1.066
4	0.082	3.5193	0.0880	13.1974	0.2092	13.4067	44.25±0.542
5	0.094	4.0343	0.1009	15.1288	0.2972	15.4260	50.91±0.538
6	0.106	4.5494	0.1137	17.0601	0.3981	17.4582	57.62±1.391
7	0.115	4.9356	0.1234	18.5086	0.5118	19.0204	62.77±1.414
8	0.119	5.1073	0.1277	19.1524	0.6352	19.7876	65.31±1.078
9	0.125	5.3648	0.1341	20.1180	0.7629	20.8809	68.91±1.043
10	0.127	5.4506	0.1363	20.4399	0.8970	21.3369	70.42±0.512
11	0.132	5.6652	0.1416	21.2446	1.0333	22.2779	73.52±1.046
12	0.133	5.7082	0.1427	21.4056	1.1749	22.5805	74.52±1.071

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Section -3, Two level full factorial tutorials, design expert software, version 6.01, user's guide.