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Research Paper

Formulation, Optimization and Evaluation of Bilayer Sustained Release Drug Delivery System of Telmisartan and Hydrochlorothiazide

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This study was performed to design bilayer tablets of Hydrochlorothiazide and Telmisartan to give immediate release of Hydrochlorothiazide and sustained release of Telmisartan. Bilayer tablets comprised two layers, i.e immediate release and controlled release layers. The immediate release layer comprised sodium starch glycolate as a super disintegrant and the sustained release layer comprised HPMC K4M and HPMC K100M as the release retarding polymers. A 3^2 full factorial design was applied to systemically optimize the drug release profile. The amounts of HPMC K-4M (X1) and HPMC K-100M (X2) were selected as independent variables. Cumulative % release of drug for 24 hours, t50% and similarity factor (f_2) were selected as dependent variables. The results of the full factorial design indicated that a low amount of HPMC K-100M and a high amount of HPMC K-4M favors sustained release of Telmisartan. After stability tests, degradation of both drugs were found but the drug contents were found to be within the range. Therefore, biphasic drug release pattern was successfully achieved through the formulation of floating bilayer tablets in this study.

Key words: Bilayer tablet, Telmisartan, Hydrochlorothiazide, controlled release layers

INTRODUCTION

Development of oral controlled release systems has been a challenge to formulation scientists because of the difficulty in localizing the system in target areas of the gastrointestinal tract. Controlled/sustained release preparations using alternating routes have also been formulated but oral route still remains preferable[1]. In recent years, peroral dosage forms for gastric retention have attracted more and more attention for their theoretical advantage in gaining control over the time and the site of drug release. This would be particularly valuable for drugs that exhibit an absorption window in the upper part of the small intestine. Various approaches have been used to prepare dosage forms for gastric retention[2] . These systems mainly consist of swelling and expanding systems[3-5], floating capsules[6,7], floating pellets[8] and floating granules[9]. Gastric retention of the drugs provides such advantages as better delivery of the drugs with narrow absorption windows in the small intestinal region, and longer residence time in the stomach, which could be advantageous for

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local action in the upper part of small intestine[10]. The current investigation aims at development of regioselective floating bilayer tablets, different release patterns of Hydrochlorothiazide (HCT). As it is the diuretic of the benzothiadiazine group and has proved very important role in the management of mild to moderate hypertension. It inhibits sodium reabsorption in the distal tubules causing increased excretion of sodium and water as well as potassium and hydrogen ions. Hydrochlorothiazide is poorly water soluble drug having plasma half life of 6-8 hrs.[11].

Telmisartan (TS) is antihypertensive agent. The major drawback of this drug is its low aqueous solubility that delays its absorption from the gastrointestinal tract. Prolonged use of the drug is associated with hypokalemia, hypotension, tachycardia and urinary tract infection[12].

In the present study, an attempt has been done to formulate a bilayer floating system of HCT and TMS. The optimized formulation was then considered for *in-vitro* buoyancy studies.

EXPERIMENTAL

Preparation of bilayer floating tablets

Bilayer floating tablets were prepared by direct compression using sodium starch glycolate as a superdisintegrant, and HPMC K4M and HPMC K100M as the release controlling polymers, and sodium bicarbonate as a gas generating agent. The optimum concentrations of the above ingredients were determined under experimental conditions and on the basis of trial preparation of the tablets. Preparation of bilayer tablets had two steps:

Preparation of immediate of release layer: The ingredients (Table 1) were accurately weighed and added into the blender in ascending order. The powder mix was blended for 20 min to obtain uniform distribution of the drug in formulation. 100 mg of the powder mix was accurately weighed and manually fed into the die on controlled release layer and compressed at a compression pressure of 3 N using 10-mm.

Table 1: Optimization of immediate release formulation

	A10	A11	A12	A13	A14	A15
Drug	25	25	25	25	25	25
Ac-di-sol	-	-	-	2.5	3	5
SSG	2.5	3	5	-	-	-
DCP	69.5	69	67	69.5	69	67
Mgstearate	1	1	1	1	1	1
Talc	2	2	2	2	2	2
Total Wt.	100	100	100	100	100	100

*All the ingredients is in mg

Preparation of the sustained release layer: The tablets were prepared by wet granulation technique. Drug and polymers were passed through 60 # sieve and then dry blend of drug were granulated with PVP K-30 as a binder which was dissolved

in isopropyl alcohol. The mass was dried at 50°C and sized through 22 # sieve. Finally, magnesium stearate were mixed as glidant, and then tablet blend was compressed on Rotary tablet compression machine (CMB4 -35 stations) using 16/32 mm, SC break line/plain.

Full factorial design

A 3^2 randomized full factorial design was used in this study. In this design 2 factors were evaluated, each at 3 levels, and experimental trials were performed at all 9 possible combinations (Table 2).

The amounts of HPMC K-4M (X1) and HPMC K-100M (X2) were selected as independent variables. Percentage release of drug for 24th hour (Q24), t50% and similarity factor (f_2) were selected as dependent variables.

Physical Characterization of the Designed Tablet:

The properties of Bilayer tablets such as hardness, friability, weight variation, and Thickness were determined using reported procedure. Tablet hardness was determined by using a Dial type hardness tester. Friability was determined by Roche friability tester at 100 rpm. The weight variation was determined by using Sartorius balance. Thickness was determined by using Vanier calipers. In-vitro disintegration test (for IR layer) was determined by using Tablet disintegration tester ED-20 (Table 3 and 4).

In-vitro dissolution profile

For HCT:

The release rate of hydrochlorothiazide from fast dissolving tablets was

Table 2: Full Factorial Design Layout

Batch No.	Variables levels in coded form		Q_{24}	$t_{50\%}$	f_2
	X_1	X_2			
F1	-1	-1	104.73	10.21	49.27
F2	-1	0	89.25	12.32	59.34
F3	-1	+1	86.83	14.25	47.58
F4	0	-1	100.34	11.07	71.21
F5	0	0	86.35	12.77	56.18
F6	0	+1	78.51	16.62	37.42
F7	+1	-1	99.92	11.46	79.79
F8	+1	0	73.14	14.66	44.09
F9	+1	+1	57.53	19.50	31.54

Translation of coded levels in actual units

Variables level	Low (-1)	Medium (0)	High (+1)
HPMC K4M (X_1)	30	40	50
HPMC K100M (X_2)	30	40	50

determined using USP Dissolution Testing Apparatus II (Paddle type). The dissolution test was performed using 900 ml of 0.1 N HCl, at 37 ± 0.50ºC and 100 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus every 2 min. for 30 min, and the samples were replaced with fresh dissolution medium. The samples were filtered through Whatman filter paper no. 41. Absorbance of these solutions was measured at 273 nm using UV spectrophotometer Shimadzu 1700.

For TMS:

Dissolution studies were performed on USP dissolution apparatus type II with 900 ml dissolution medium Phosphate buffer (pH 7.5) at 37°C±0.5°C at 75 rpm for 45 min. At fixed time intervals, 5 ml aliquots were withdrawn, filtered, suitably diluted, and assayed for TMS content by measuring the absorbance at 297 nm.

Equal volumes of fresh medium (pre-warmed to 37°C) were replaced into the dissolution medium to maintain constant volume throughout the test period. Dissolution studies were performed in six replicates, and calculated mean values of cumulative drug release were used while plotting the release curves.

Table 3: Physical Parameters of Prepared Tablet Containing HCT

Formulation	Disintegration Time (sec)	Hardness (kg/cm^2) Mean (n=20)	Weight variation (mg) (n=20)	Thickness mm(n=10)	% Friability (n=20)
A10	7 ± 0.132	4.5 ± 0.065	100 ± 0.564	2.78 ± 0.12	0.25 ± 0.001
A11	6 ± 0.016	4.0 ± 0.016	100 ± 0.324	2.67 ± 0.15	0.37 ± 0.031
A12	5 ± 0.096	3.5 ± 0.025	99 ± 0.652	2.55± 0.09	0.34 ± 0.043
A13	8 ± 0.127	4.5 ± 0.021	100 ± 0.464	2.89 ± 0.11	0.56 ± 0.021
A14	7 ± 0.133	4.0 ± 0.032	100 ± 0.512	2.70 ± 0.13	0.61 ± 0.035
A15	6 ± 0.076	4.0 ± 0.041	101 ± 0.624	2.64 ± 0.05	0.43 ± 0.022

Table 4: Physical parameters of prepared tablet containing TMS

Batches	Weight variation (mg) (n=20)	Hardness (kg/cm^2) (n=10)	Friability (%) (n=10)	Thickness mm(n=10)
F1	355 ± 2.82	4.8 ± 0.167	0.73 ± 0.0028	3.65 ± 0.05
F2	357 ± 2.51	4.4 ± 0.357	0.87± 0.0018	3.70 ± 0.12
F3	355 ± 2.54	5.5 ± 0.257	0.85 ± 0.0023	3.75± 0.07
F4	354 ± 2.74	4 ± 0.135	0.83 ± 0.0018	3.60 ± 0.17
F5	354 ± 2.88	5 ± 0.156	0.89 ± 0.0015	3.75 ± 0.09
F6	355 ± 2.54	5.5 ± 0.057	0.68 ± 0.00149	3.85 ± 0.04
F7	355 ± 2.53	6 ± 0.175	0.86 ± 0.0018	3.80 ± 0.10
F8	355 ± 2.88	4 ± 0.127	0.94 ± 0.0028	3.75 ± 0.15
F9	354 ± 2.71	5 ± 0.145	0.86 ± 0.0018	3.78 ± 0.18

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RESULT AND DISCUSSION:

For IR layer of HCT

All the tablet formulations showed acceptable pharmacotechnical properties and complied with the in-house specifications for weight variation, hardness and friability. Results are shown in Table 3.Hardness is in between 3.5 ± 0.025 to 4.5 ± 0.065 kg/cm^2 is sufficient to prevent breaking of tablets in handling as well as during packaging. Friability below 1 % prevents loss of material during handling. Weight variation is also important consideration, which is ultimately responsible for content uniformity is in between 99 ± 0.652 to 101 ± 0.624 mg. Disintegration time is in between 5 ± 0.096 to 8 ± 0.127 second which is very much important parameter for IR tablet. Prepared tablets were evaluated for *in-vitro* dissolution profile. Graphical presentation of drug release data for batch A10 to A15 is shown in Figure 1

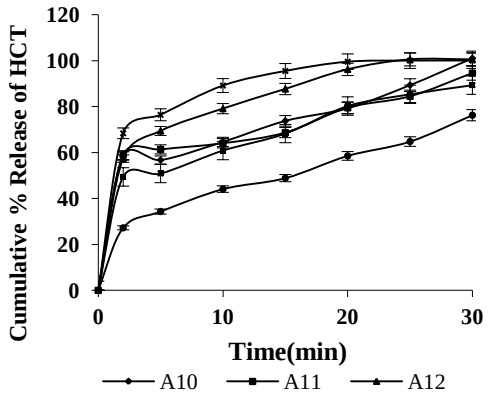

Fig. 1: Drug release profile of immediate release formulation of HCT

In case of batch A12, release of drug was 99.56% within 20 minutes (5% of SSG).Due to it fast release of drug within stipulated period of time, batch A12 were selected as an optimized batch.

For SR layer of TMS
Full factorial design

Factorial equation for Q_{24}

Concerning Q_{24}, the results of multiple linear regression analysis showed that both the coefficients b_1 and b_2 bear a negative sign. It is possible that at higher polymers concentration, TMS is trapped in smaller polymer cells and it is structured by its close proximity to the polymer molecules. So, increasing the amount of the polymer in the formulations increased the time it took for the drug to leave the formulation and retard release of drug into the medium.

$$Q_{24Hrs} = 84.91 - 8.53 X_1 - 13.8X_2 - 5.87X_1X_2 - 3.29X_1^2 + 5.23X_2^2 \quad (3)$$

($R^2 = 0.9829$)

The Q_{24} for all the batches F_1 to F_9 varied from 57.53 % to 104.73 % (Table 2) showed good correlation coefficient as 0.9829. Results of the equation (3) indicated that both the concentration of the X_1 and X_2 were responsible for the Q_{24}, but the effect of the concentration of HPMC K4M (X_1) was very high than the effect of the concentration of HPMC K100M (X_2). (Figure 2)

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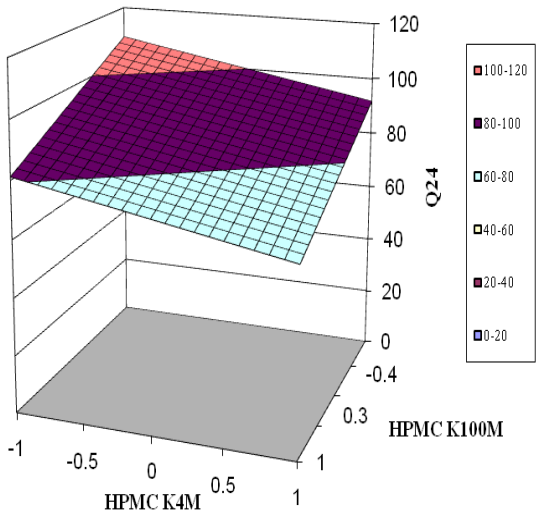

Fig.2: Effect of variable on Q24

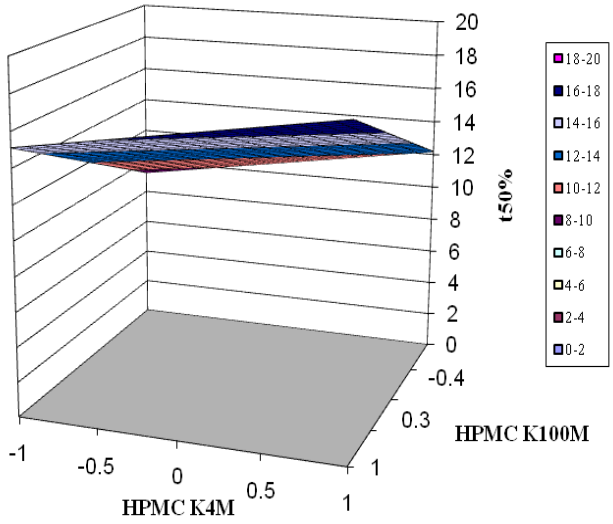

Fig. 3: Effect of variable on t50%

Factorial equation for t50%

The t50% for all the batches F_1 to F_9 varied from 10.21% to 19.50 % (Table 2). Therefore, increasing the concentration of either HPMC K-4M or HPMC K-100M is expected to decrease t50%. The fitted equation relating the response t50%to the transformed factor is shown in following equation,

$$t_{50\%} = 13.08 + 1.47X_1 + 2.93X_2 + 1.0X_1X_2 + 0.24X_1^2 + 0.60X_2^2 \ldots\ldots\ldots\ldots\ldots\ldots (4)$$

$$(R^2 = 0.9910)$$

From the above equation, it was concluded that the effect of the concentration of HPMC K100M (X_2) was high than the effect of the concentration of HPMC K4M (X_1) for t50%. (Figure 3)

Factorial equation for f_2

The similarity factor, f_2, given by SUPAC guidelines for modified release dosage form was used as a basis to compare dissolution profiles. The dissolution profiles are considered to be similar when f_2 is between 50 and 100.The f_2 value for all the batches F_1 to F_9 varied from 31.45 to 79.79 (Table 2).

$$f_2 = 55.20 - 0.12X_1 - 13.9X_2 - 11.64X_1X_2 - 3X_1^2 - 0.40X_2^2 \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (5)$$

$$(R^2 = 0.947)$$

In-vitro drug release profile of all batches of factorial design was compared with theoretical drug release profile.

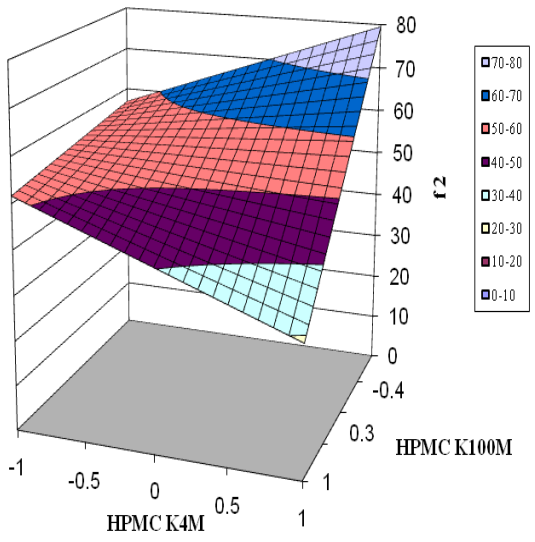

Fig. 4: Effect of variable on f_2

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The result is shown in Table 2, which indicates that, the all the batches shows good similarity to theoretical release profile. But batch F7 showed the highest f_2 among all the batches that is 79.79. (Fig. 4)

In-vitro dissolution studies

Dissolution profiles of TMS Sustained Release Matrix tablets of factorial batches are shown in Figure 5. From the release profile we can see that batch F_9 shows release of drug 57.53 % at 24 hour. Whereas, batch F_1 shows that release of drug at 24 hours 104.73%.

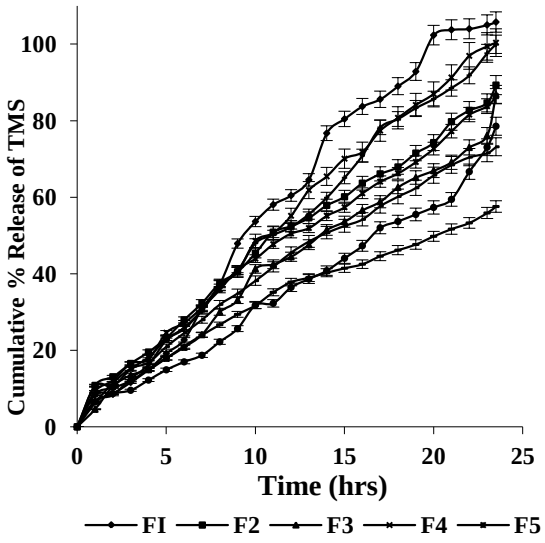

Fig. 5: Drug release profile of sustain ed release formulation of TMS(F1-F9)

So, it can be concluded that at higher polymer concentration release of drug may be retarded. Batch F_7 was optimized for the final formulation shows 99.92 % release of drug at 24 hours.

Kinetic study of optimized batch F7

The results of F-statistics were used for the selection of the most appropriate model. The goodness of fit test proposed by Bamba and Co-workers was used to determine the kinetics of drug dissolution profile. The release profile of the best batch (F7), which showed highest similarity factor f_2, was fitted to Zero-order (F= 4.07). Priority should be given to the model with the least F-value. Thus, it may be concluded that the drug release from sustained release tablet of TMS is best explained by Zero-order reaction shown in Table 5.

Table 5: Kinetic modeling data of batch F7

Model	Zero-order	First-order	Higuchi plot	Korsmeyer
F-Value	4.07	1139.38	58.21	4.12
R^2	0.9980	-0.7869	0.9710	0.9938
Slope	4.23	-0.1631	23.51	0.9398
Intercept	1.35	5.33	-23.65	-1.4839

Accelerated stability study of prepared bi-layer tablet (BT)

Sample withdraws at the interval of one month for three months showed no change in *in-vitro* drug release profile (Figure 6). % Assay shows 99.79 (initial), 98.34 (after 1 month), 97.29 (after 2 month) and 97.00 (after 3 month). Results of the stability study shoe no remarkable change in the release profile of the TMS Sustained Release Matrix tablet after the stability.

CONCLUSION

In formulation of IR layer of HCT, it can be concluded that role of superdisintegrant plays an important role. At higher Conc.

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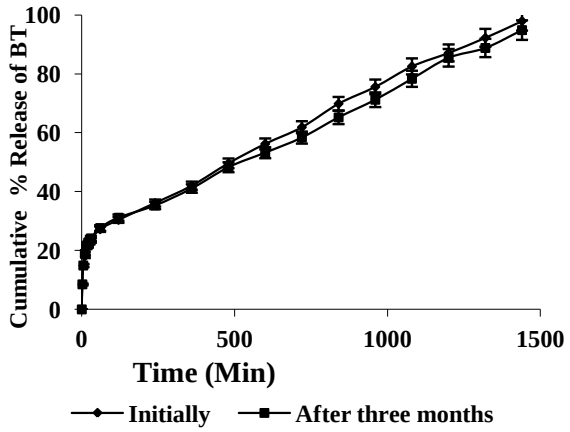

Fig. 6: Drug release profile of prepared bi-layer tablet before and after stability study

of SSG (5 %), better disintegration time was obtained.In formulation TMS Sustained Release Matrix Tablet, a 3^2 full factorial design was employed for preparation of tablets possessing optimized characteristics (batches F_1 to F_9). The amount of HPMC K-4M(X_1) and HPMC K-100M (X_2) were selected as independent variables. Cumulative % drug release at 24 hours, t50% and similarity factor *f2* selected as dependent variable. Based on result of multiple linear regression analysis, it was concluded that role of polymer concentration is very important in this formulation. So, we can conclude that drug and other excipients are compatible which each other. Drug was released from bi-layer tablet by Zero-order kinetics, which suggests concentration independent release pattern via diffusion mechanism. Prepared bi-layer tablet passed all the pharmacopeial specifications. Stability study of final prepared bi-layer tablet after three month showed no change *in-vitro* drug release profile. It was concluded that by adopting a systematic formulation approach, an optimum point could be reached in the shortest time with minimum efforts.

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