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Research Article

DEVELOPMENT AND OPTIMIZATION OF BILAYER HYDRODYANAMICALLY BALANCED SYSTEM OF AMLODIPINE BESYLATE IMMEDIATE RELEASE AND HYDROCHLOROTHIAZIDE CONTROLLED RELEASE

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ABSTRACT

Objective: An effervescence based hydrodynamically balanced system of bilayer tablet formulation is developed with an aim to achieve the immediate release of Amlodipine Besylate (AB) and sustained release for Hydrochlorothiazide (HCTZ).
Methods: The bilayer system was developed with one layer acting as a gas generating layer (Layer 1) and the second layer acting as the sustained release layer (Layer 2). AB was incorporated in Layer 1 and was targeted to release > 85% (Q) within 15 minutes. HCTZ was incorporated in Layer 2 and was targeted to release over a period of 8 hour.
Results and conclusion: Water soluble matrix polymers Methocel K4M and Methocel K15M were used in combination in the sustained release layer. The ratio of K4M and K15M was optimized to achieve the target dissolution profile. The targeted release rate was in the range of 8 to 10 %/hour.

Keywords: Amlodipine besylate (AB), Hydrochlorothiazide (HCTZ), HPMC K4M, HPMC K15M, hydrodynamically balanced bilayer tablets, target dissolution profile.

INTRODUCTION

Amlodipine Besylate (AB) is a long-acting calcium channel blocker used as an antihypertensive and in the treatment of angina pectoris. It acts by relaxing the smooth muscle in the arterial wall, decreasing total peripheral resistance thereby reducing blood pressure [1-3]. One of the most common adverse effects of Amlodipine Besylate is peripheral edema hence it is preferably used in combination with a diuretic like Hydrochlorothiazide (HCTZ) which can prevent the peripheral edema Also, the combination of AB and HCTZ is reported to be synergistic in controlling the blood pressure [4, 5]. One potential problem of this combination is the extreme difference in the plasma half life of both the drugs. While AB has a reported half life of 30 to50 hours, HCTZ has t1/2 of only 5.6 to 14.8 hours. Hence there is a strong rational for developing a fixed dose combination of an immediate release AB and controlled release HCTZ tablets. Again, HCTZ has a reported variability in absorption from the intestine making it as an ideal candidate for a gastro retentive drug delivery system [6]. The aim of the current work was to develop a bilayer floating drug delivery system in which one layer comprises of the gas generating layer [7] and the second layer comprises of the controlled release layer. The AB portion of the fixed dose combination was incorporated in the gas generating layer and the HCTZ portion was part of the controlled release layer, the floating lag time, total floatation time and the in vitro drug release of AB and HCTZ were optimized by using a combination of different viscosity grades of HPMC polymers [8]. The Targeted Product Profile (TPP) is mentioned in Table1

Table 1: Target Product Profile

Floating lag time	Not more than 90 seconds
Total floatation time	Not less than 8 hours
Dissolution test specifications for AB	
Time (Minute)	Mean % AB dissolved
0	0
30	Not less than 80% (Q)
Dissolution test specifications HCTZ controlled release	
Time(hours)	Mean % HCTZ dissolved
0	0
1	15-40
2	35-60
4	50-70
8	65-85
10	>85

MATRERIALS AND METHODS

Chemicals and Reagents

Amlodipine besylate (AB, USP, EMCO Industries, Hyderabad, India), Hydrochlorothiazide (HCTZ, USP, EMCO Industries Hyderabad, India), HPMC K4M, HPMC K15M, HPMC K 100M (Methocel, Dow Chemical's USA), Microcrystalline cellulose USP (Avicel PH 102, FMC, USA), Magnesium stearate USP (Ferro, US), Poly Vinyl Pyrrolidone PVP K 30 USP (Ashland Specialty Chemicals, US), sodium bicarbonate GR (Merck, India), anhydrous citric acid GR (Merck, India) All other chemicals and reagents used were of Analytical Reagent grade from Merck. Purified water USP (from Millipore system) was used where ever required.

Experimental

Bilayer tablets of 500 mg weight were prepared by the direct compression method. The composition is given in table 2

Direct compression process was followed. The tablets were compressed on 10.5 mm circular biconvex die/punch set using Rimek MiniPress-II MT 12 station rotary compression machine (KYRNAVATI Engineering, Ahmadabad, India). The machine was manually operated to compress the bilayer tablets. The compression force was set in such a way that all formulations were compressed at hardness of 60 to 80 N. All batches were evaluated for physical parameters, assay and uniformity of content. Each batch (at n=3) was subjected to 10 hours dissolution profile testing in 0.1N Hcl using USP Type I apparatus at 50 rpm (ELECTROLAB, TDT-08L, India).Aliquots of 5 ml were withdrawn at 5, 10, 15, 30 and 60 minutes for first 1 hour and then at 120, 240, 360, 480 and 600 minutes thereafter. The samples were analyzed for % drug dissolved using UV spectrophotometer (LABINDIA® UV 3000+ software UV win 5 software v 5.2.0, Mumbai, India). The analytical method followed was based on the principal that AB shows fluorescence at 365 nm in 0.1N Hcl while HCTZ does not exhibit this phenomenon (Fig.1). Consequently a simultaneous estimation method was developed in which AB was measured at 365 nm and HCTZ was

measured at 270 nm from the same sample. No interference of either of the components or any of the excipients was observed at these two wavelengths

Table 2: Unit composition formulae

	Floating IR layer composition									SR layer composition				
	AB (mg)	**NaHco₃ (mg)**	**Citric acid (mg)**	**MCC-102 (mg)**	**PVP K-30 (mg)**	**Mg. Stearate (mg)**	**HCTZ (mg)**	**HPMC K4M (mg)**	**HPMC K15M (mg)**	**HPMC K100M(mg)**	**PVP K-30 (mg)**	**NaHco3 (mg)**	**Mg.Stearate (mg)**	**MCC-102 (mg)**
Optimization Of AB floating layer														
F1	6.94	64	22	137	15	5	12.5	75	75	-	12.5	-	5	70
F2	6.94	106	22	95	15	5	12.5	75	75	-	12.5	-	5	70
F3	6.94	128	22	73	15	5	12.5	75	75	-	12.5	-	5	70
Optimization of HCTZ sustained release layer														
	AB (mg)	**NaHco₃ (mg)**	**Citric acid (mg)**	**MCC-102 (mg)**	**PVP K-30 (mg)**	**Mg. Stearate (mg)**	**HCTZ (mg)**	**HPMC K4M (mg)**	**HPMC K15M (mg)**	**HPMC K100M(mg)**	**PVP K-30 (mg)**	**NaHco3 (mg)**	**Mg.Stearate (mg)**	**MCC-102 (mg)**
F4	6.94	106	22	95	15	5	12.5	25	25	25	12.5	-	5	175
F5	6.94	106	22	95	15	5	12.5	50	50	50	12.5	-	5	70
F6	6.94	106	22	95	15	5	12.5	25	25	-	12.5	-	5	170
F7	6.94	106	22	95	15	5	12.5	40	40	-	12.5	-	5	140
F8	6.94	106	22	95	15	5	12.5	60	60	-	12.5	-	5	100
F9	6.94	106	22	95	15	5	12.5	75	75	-	12.5	-	5	70
F10	6.94	106	22	95	15	5	12.5	50	50	-	6	6.5	5	120
F11	6.94	106	22	95	15	5	12.5	55	55	-	6	6.5	5	110
F12	6.94	106	22	95	15	5	12.5	60	60	-	6	6.5	5	100
F13	6.94	106	22	95	15	5	12.5	65	65	-	6	6.5	5	90

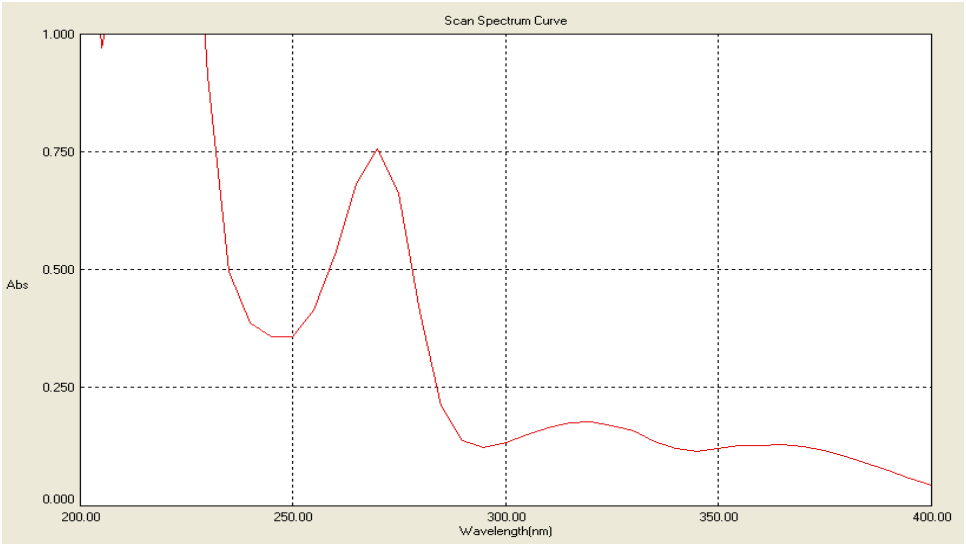

Fig.1: UV spectra of a mixture of HCTZ (270 nm) and AB (365 nm) (10 µg/ml each)

Table 3: Physical Properties and Assay of all batches of Bilayer floating tablets

Formulation code	Lag time	Log time	Hardness (N)	Friability (% w/w)	Assay
F4	>90 sec	Does not float	30	0.871	95-97.5%
F5	5 sec	< 8 hrs, Fails	40 - 45	0.654	94.5-98.2%
F6	>90 sec	Does not float	30-40	0.557	94.8-96.4%
F7	25 sec	< 8 hrs, Fails	30-45	0.607	97.1-99%
F8	3 min	< 8 hrs, Fails	35-55	0.465	94.3-97%
F9	4 min	< 8 hrs, Fails	55-60	0.323	98.7-99.1%
F10	25 sec	>12 hrs	70-80	0.201	95.9-99.3%
F11	25 sec	>12 hrs	70-80	0.235	96.6-97.2%
F12	30 sec	>12 hrs	80-90	0.208	97.3-96%
F13	40 sec	>12 hrs	80-90	0.212	95-98%

RESULTS AND DISCUSSION

The physical parameters of all batches including the tablet hardness, floating lag time, total floatation time, friability and assay values are given in Table 3[9, 10, and 11]

Formulations F1 to F3 were fabricated to optimize the composition of the floating layer. It was observed that formulation F2 gives tablets which have floating lag time within the specifications. Hence this composition was finalized for all further trials. For formulations F4 to F9 were failing in either floating lag time (F4) or total floatation time (F5 to F9) also, all formulations had significantly low hardness levels. Hence these were not considered for in vitro dissolution testing. In case of formulation F10, a part of PVP was replaced with sodium bicarbonate and the targeted total floatation time of > 8 hours was achieved. Hence all formulations from F10 to F13 sodium bicarbonate were added to the HCTZ. The hardness levels for all tablets in these formulations were in the range of 70 to 90 N which is acceptable for tablets of this size. The dissolution of immediate release AB is shown in Fig 2.

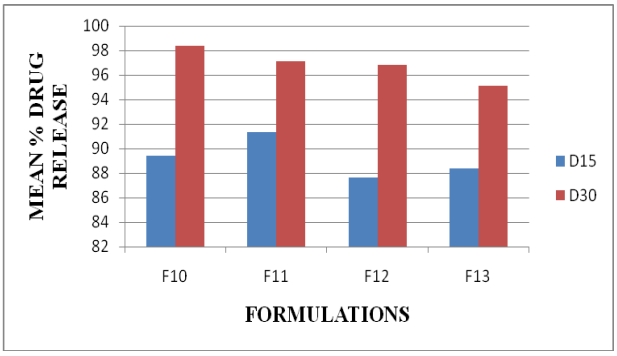

Fig 2: Comparative release of Amlodipine Besylate at 15 minutes and 30 minutes time points

The drug release for AB from F10 to F13 is similar. > 85% of drug release is achieved within 15 minutes. Thus the release for AB seems to be independent on the composition of the SR layer and is solely driven by the disintegration of the gas generation layer of the bi layer system.

The in vitro dissolution profiles for HCTZ from formulations F10 to F13 in comparison to the TPP are shown in Fig 3.

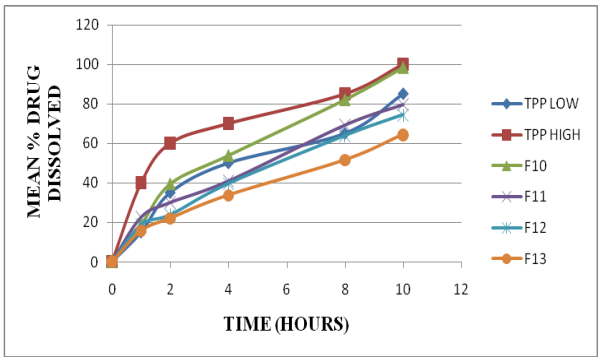

Fig 3: *in vitro* Dissolution profile for HCTZ from formulations F10 to F13, comparison with the TPP

The comparative in vitro dissolution values for 1hour (D1), 4 hours (D4) and 8 hours (D8) against the targeted values is shown in Fig 4.

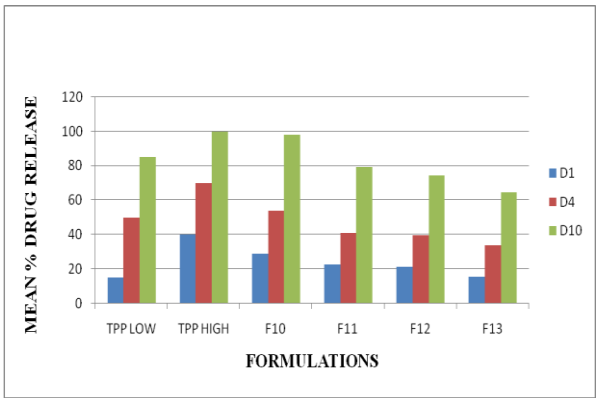

Fig 4: Comparison of HCTZ release rate and extent from F10 to F13 with TPP

This indicates that only in case of F10, dissolution profile is matching to the Target profile. All other formulations are significantly slower than the target profile.

The release rate kinetics for F10 was calculated and was shown to follow the Korsmeyer- Pappas model for defining the kinetics of the drug release [12]. This indicates that the mechanism of drug release from the hydro dynamically balanced Bilayer matrix system is primarily by combination of diffusion and swelling. Then total polymer concentration required for optimum drug release is 40% and it is achieved by using a combination of K4M and K15M.

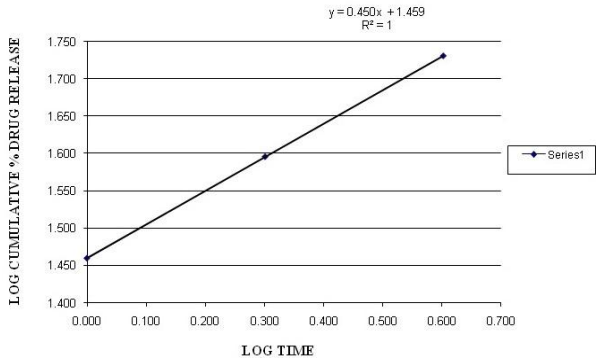

Fig4: The Korsmeyer-peppas release rate kinetics for release of HCTZ from formulation F10

CONCLUSIONS

- Bilayer floating drug delivery system for fixed dose combination of AB and controlled release HCTZ was successfully formulated.
- The system was formulated to have a gas generating release of AB.
- Amlodipine fraction of the composition released > 80% (Q) of AB within 15 minutes irrespective of the controlled release fraction of the dosage form.
- HCTZ controlled release was achieved by using a combination of HPMC K4M and HPMC K15 M used at the level of 20% w/w of each polymer with respect to the final weight of the tablets.
- Further scale up work, stability testing and in vivo studies are under progress.

Abbreviations

AB: Amlodipine Besylate
HCTZ: Hydrochlorothiazide
HPMC: Hydroxy Propyl Methyl Cellulose
TPP: Targeted Product Profile

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