Research Article

FORMULATION AND EVALUATION OF BILAYERED TABLETS OF METFORMIN HYDROCHLORIDE AND ATORVASTATIN CALCIUM

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ABSTRACT

The objective of the study was to develop a bilayer tablets consisting of Atorvastatin calcium as an immediate release layer and Metformin hydrochloride as a sustained release layer. Granules of different formulations of both the drugs were evaluated for bulk density, tapped density, compressibility index and Hausner's ratio. The prepared bilayer tablets were evaluated for weight variation, thickness, hardness, friability, drug content and *in vitro* drug release. The *in vitro* release profile showed the desired biphasic behavior. The Metformin hydrochloride released for more than 12 hrs, where as Atorvastatin calcium dissolved within 45 min. Bilayer tablet prepared from optimized formula (Trial 10) was found to be best suited method for fixed dose combination of sustained release Metformin Hydrochloride and immediate release Atorvastatin calcium.

Keywords: Bilayer tablet, Atorvastatin calcium, Metformin hydrochloride, NIDDM, Hyperlipidemia, Sustained release.

INTRODUCTION

Developed and developing countries move towards combination therapy for treatment of various diseases and disorders requiring long term therapy such as hypertension and diabetes. Combination therapy has various advantages over monotherapy such as less dose dependent side effects. Further, low dose combination of two different drugs minimizes the clinical and metabolic effects that occur with maximal dosage of individual component of the combined tablet and thus dosage of the single component can be reduced. Hence bilayered tablets are prepared for treating two different diseases with one unit dosage form. This dosage form has the advantage of separating two incompatible drugs with inert barrier between them. Incompatible drugs can be separated by formulating them in separate layers as a two layer tablets or separating the two layers by a third layer of an inert substance as a barrier below the two[1]. Bi-layered tablets refers to tablet containing subunits that may be either the same or different. Bi-layered tablets allows for designing and modulating the dissolution and release characteristics and they are prepared with one layer of drug for immediate release while second layer designed to release drug latter, either as second dose or in an sustained release manner. Similarly one drug can be administered for immediate release and another drug can be for sustained release[2].

The primary objective of sustained release drug delivery is to ensure safety and to improve efficacy of drugs as well as patient compliance. If the drug is given in conventional dosage form, it has to be administered several times a day to produce the desired therapeutic effect. The pronounced fluctuations resulting from the conventional drug administration are likely to yield of no therapeutic effect when drug concentration fall below minimum therapeutic level[3]. In this context sustained drug delivery system is designed to reduce the frequency of dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. In an approach, polymers and their blends are used in various formulations to achieve sustained drug release. Most thoroughly investigated and used synthetic agents are hydrogenated castor oil, hydroxy propyl methyl cellulose and sodium carboxy methyl cellulose[4].

Diabetes is a disease noted as one of the leading causes of death and disability worldwide. India has highest number of diabetic patients in the world. It has been estimated that by 2025 there will be more than 57.2 million cases of diabetes. Non insulin dependent diabetes mellitus (NIDDM) is associated with a two to fourfold increased risk of both coronary heart disease and stroke. Findings of observational studies suggest that lipid lowering should have an important place in the primary prevention of cardiovascular disease in people with diabetes[5,6,7]. Helen et al.,[8] reported that lipid lowering drug like Atorvastatin calcium is safe and efficacious in reducing the risk of cardiovascular disease including stroke in diabetes patients, on the other hand biguanides like Metformin is widely used to treat NIDDM. In this context this study was focused to formulate and evaluate bilayer tablets of Metformin hydrochloride as sustained release layer and Atorvastatin calcium as an immediate release layer to develop polytherapy for the treatment of NIDDM and hyperlipidemia.

MATERIALS AND METHODS

Materials

Metformin hydrochloride and Atorvastatin calcium were received as gift samples from Dr. Reddy's Laboratories Ltd., Hyderabad. All other materials like micro crystalline cellulose (MCC), lactose, povidone, sodium starch

glycolate, magnesium stearate, polysorbate, hydroxyl propyl methyl cellulose (HPMC), hydroxy propyl cellulose (HPC), hydrogenated castor oil, sodium starch glycolate, calcium carbonate, quinoline yellow, isopropyl alcohol were obtained from commercial sources. All reagents used in these experiments were analytical grades.

Methods

Preparation of bilayer tablets: Two granulations such as immediate release granules containing Atorvastatin calcium and sustained release granules containing Metformin were prepared by wet granulation method using granulating agent according to the formula given in the Table 1. First sustained release layer (Metformin hydrochloride) was prepared by taking appropriate quantities of the ingredients as mentioned in the formula. These ingredients were screened through sieve no.40, isopropyl alcohol and water in the ratio of 9:1 was added to weighed quantity of povidone slowly with continuous stirring. The drug and retardant were mixed slowly by using binder solution. Then the wet mass is passed through the sieve to get granules and obtained granules were dried and sifted through sieve no.20. Finally HPMC K 100 CR, MCC 102 and magnesium stearate were added to the above sifted granules and blended for few min before compression.

Table 1: Composition of various Formulations

Ingredients ↓	First Layer (mg/tablet)						Second Layer (mg/tablet)			
Trial No →	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Metformin HCl	500	500	500	500	500	500	500	500	500	500
Hydrogenated castor oil	321	---	---	---	---	---	---	---	---	---
Ethyl cellulose	---	44	---	---	---	---				
Povidone K 90 D	25	---	63	110	85	85	85	85	85	85
HPMC K 100 M	---	250	110	155	180	---	---	---	---	---
Isopropyl alcohol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Purified water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
MCC 102	---	---	---	---	150	150	150	150	150	150
Sodium CMC	---	---	90	---	---	---	---	---	---	---
Magnesium stearate	4	5	7	5	5	5	5	5	5	5
HPMC K 15 M	---	51	---	---	---	---	---	---	---	---
HPMC K 100 M	---	---	80	80	30	---	---	---	---	---
HPMC K 100 M CR	---	---	---	---	---	210	210	210	210	210
Atorvastatin calcium	---	---	---	---	---	---	10	10	10	10
Lactose	---	---	---	---	---	---	50	69.73	67	67
MCC 114	---	---	---	---	---	---	89.73	120	103.5	103.5
HPC	---	---	---	---	---	---	5	5	7.5	7.5
Poloxamer	---	---	---	---	---	---	3	3	---	---
Meglumine	---	---	---	---	---	---	8	8	---	---
Purified water	---	---	---	---	---	---	q.s.	q.s.	---	q.s.
MCC 102	---	---	---	---	---	---	16	16	16	16
Quinoline yellow ws	---	---	---	---	---	---	0.27	0.27	0.5	0.5
Magnesium steartae	---	---	---	---	---	---	2	2	2	2
Na. starch glycolate	---	---	---	---	---	---	16	16	16	16
Calcium carbonate	---	---	---	---	---	---	---	---	22.5	22.50
Polysorbate	---	---	---	---	---	---	---	---	5	5
Isopropyl alcohol	---	---	---	---	---	---	---	---	q.s.	---

Similarly second layer Atorvastatin calcium was prepared by using appropriate quantities of ingredients as mentioned in the formula. All the excipients except quinoline yellow were sifted through sieve no.40. To the mixture of polysorbate 80 and water, HPC was added and stirred continuously to get a clear solution. Weighed quantities of MCC 114, Lactose and Atorvastatin calcium were sifted through sieve no.40 and the above prepared binder solution was added slowly to get a desired mass and the wet mass passed through the sieve to get desired granules and the obtained granules were dried and passed through sieve no.30. Finally MCC 102, calcium carbonate, sodium starch glycolate, quinoline yellow and magnesium stearate were added and blended for 5 min.

Accurately weighed quantity of immediate release and sustain release granules were compressed on bilayer compression machine (Rimek, Ahmedabad) using 20x9 mm caplet shape punches.

Evaluation of Blends[4, 9, 10]

Prior to the compression of both granules into tablets, the granules were evaluated for properties like bulk density, tapped density, compressibility index and Hausner's ratio. Physical characteristics of granules of Metformin

hydrochloride blend and Atorvastatin calcium blend were shown in table 2 and table 3 respectively.

Particle size distribution:

The particle size distribution was measured using sieve analysis method.

Density:

The loose bulk density (LBD) and tapped bulk density (TBD) were determined and calculated using the following formulas.

LBD = weight of the powder / initial volume

TBD = weight of the powder / final volume

Compressibility:

The compressibility index was determined by Carr's compressibility index.

Carr's index = $[(TBD - LBD) \times 100/TBD]$

Hausner's ratio: Hausner's ratio = TBD / LBD

Evaluation of tablets[4, 11-13]

The prepared bilayer tablets were evaluated for weight variation, thickness, hardness, friability, drug content and dissolution test were shown in Table 4, 5 and 6.

Weight variation: Twenty tablets were selected at random and the average weight was determined. Not more than two of the individual weights deviate from the average weight by more than the percentage deviation as per IP and none deviates by more than twice the percentage. IP official limit of percentage deviation for all trials is ±5%.

Thickness, Hardness, Friability: Tablets were evaluated for thickness, hardness and friability using Vernier caliper scale, Monsanto hardness tester and Roche friabilator respectively.

Drug content: The total amount of drugs within the tablets was analyzed by using UV Spectrophotometer with suitable dilution at 274 nm for Metformin hydrochloride and 246 nm for Atorvastatin calcium.

Table 2: Physical characteristics of granules of Metformin HCl blend

Powder Blend	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Compressibility index (%)	Hausner's ratio
Trial 1	0.4540	0.5679	20.05	1.25
Trial 2	0.4497	0.5579	19.40	1.24
Trial 3	0.4326	0.5301	18.39	1.22
Trial 4	0.4814	0.5132	18.97	1.36
Trial 5	0.4963	0.5842	17.95	1.16
Trial 6	0.4126	0.5754	19.23	1.26
Trial 7	0.4849	0.5874	17.44	1.21
Trial 8	0.4729	0.5621	15.86	1.18
Trial 9	0.4885	0.5857	16.59	1.19
Trial 10	0.4789	0.5654	16.89	1.18

Table 3: Physical characteristics of granules of Atorvastatin calcium blend

Powder Blend	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Compressibility index (%)	Hausner's ratio
Trial 7	0.4758	0.5042	15.94	1.18
Trial 8	0.4529	0.6926	17.62	1.21
Trial 9	0.4132	0.5321	18.81	1.23
Trial 10	0.4698	0.6084	19.56	1.24

Table 4: Evaluation Parameters of Tablets

Formulation	Thickness (mm)	Weight variation (mg)	Hardness (kg/cm$^{2)}$	Friability (%)	Drug content
Trial 1	6.5-6.8	838-857	24.8-28.4	0.002	95.23
Trial 2	6.4-6.9	841-858	26.3-31.5	0.004	96.33
Trial 3	6.5-6.7	845-856	29.4-31.7	0.001	98.32
Trial 4	6.2-6.6	844-857	31.2-32.4	0.003	97.25
Trial 5	7.3-7.8	946-953	29.6-32.4	0.004	96.45
Trial 6	7.4-7.7	943-958	28.9-32.1	0.002	99.45
Trial 7	7.02-7.08	1148-1156	NA	NA	96.75
Trial 8	7.56-7.68	1196-1204	28.6-30.5	0.003	98.43
Trial 9	7.45-7.75	1198-1208	29.5-31.5	0.0054	98.57
Trial 10	7.24-7.55	1192-1207	28.4-30.8	0.0024	98.72

Table 5: Dissolution profile of various Metformin HCl formulations

Time (hr)	Innovator (Metformin)	% Drug release of Metformin HCl					
		Trail 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6
0	0	0	0	0	0	0	0
2	43	38	48	41	39	41	42
4	59	54	66	65	62	63	60
8	83	79	89	81	78	74	82
12	103	92	112	101	101	96	102

Table 6: Dissolution profile of various Atorvastatin formulations

Time (min)	Innovator (Atorvastatin)	% Drug release of Atorvastatin			
		Trial 7	Trial 8	Trial 9	Trial 10
0	0	0	0	0	0
10	87	87	88	89	92
15	89	89	91	92	93
30	91	91	94	95	95
45	92	92	95	95	96

Dissolution test: Dissolution test of the tablets were performed using USP dissolution apparatus II (paddle) at 100 rpm and 37±0.5°C temperature and pH 6.8 phosphate buffer. Test sample (5ml) was withdrawn at particular time interval and replaced with fresh dissolution media maintained at the same temperature and the concentration of dissolved drug was determined using ultraviolet (UV) spectrophotometer at λ_{max} 232 nm for Metformin hydrochloride and 246 nm for Atorvastatin calcium. The release profile of the drugs shown in Table 5, 6 and Fig. 1, 2, 3 and 4.

Figure 1: Comparative dissolution profile of Metformin hydrochloride in Trial 1, 2 and 3 with Metformin innovator

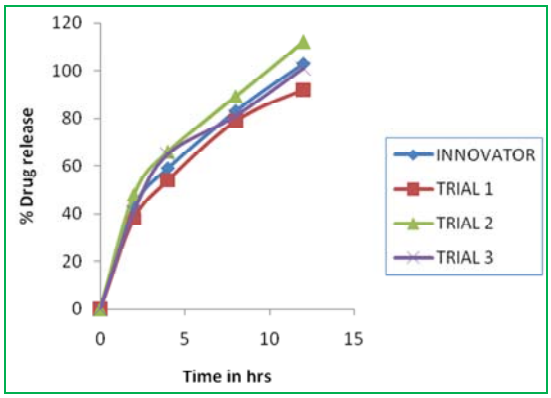


Figure 2: Comparative dissolution profile of Metformin hydrochloride in Trial 4, 5 and 6 with Metformin innovator

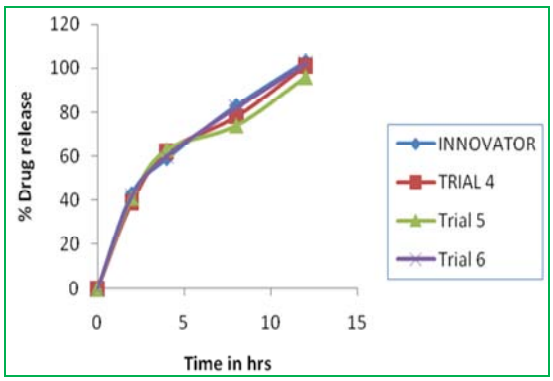


Figure 3: Comparative dissolution profile of Atorvastatin calcium in Trial 7 and 8 with Atorvastatin innovator

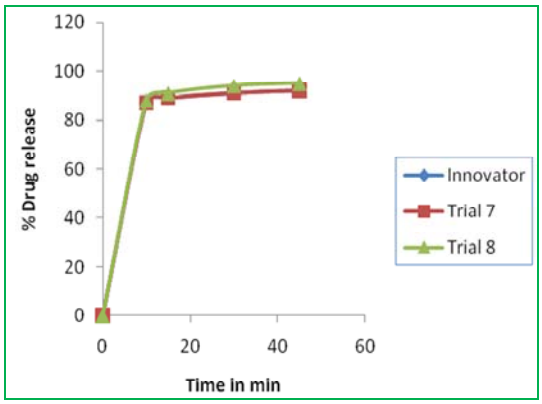
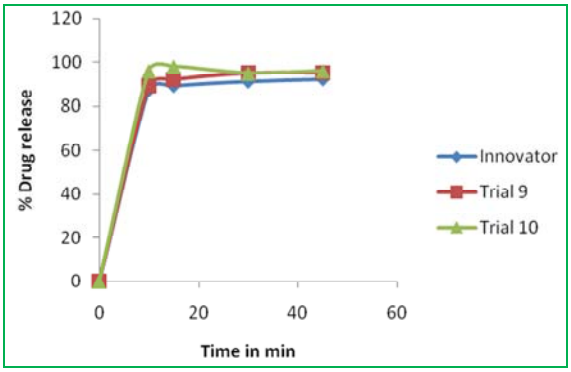


Figure 4: Comparative dissolution profile of Atorvastatin calcium in Trial 9 and 10 with Atorvastatin innovator



RESULTS AND DISCUSSIONS

In the present study various bilayered tablet formulations were prepared and evaluated with an aim of immediate release of Atorvastatin calcium and sustained release of Metformin hydrochloride. As per USP specifications not less than 80% of the drug should be released in the eighth hour for Metformin, so that the metformin hydrochloride concentration in the body can be maintained for 12 hrs since it has elimination half-life of 6.2 hrs. In the present study Metformin hydrochloride and Atorvastatin calcium bi-layered were prepared to optimize immediate release of Atorvastatin calcium and sustained release of Metformin hydrochloride by wet granulation process by

using the ingredients shown in Table.1. Six formulations (Trial 1 to Trial 6) containing sustained release granules were prepared as described earlier. Preformulation parameters such as bulk density, tapped density, Hausner's ratio, compressibility index were evaluated (Table 2), which gives the basis for the optimization of drug product quality. All the granules indicated good fine flow property. Hausner's ratio for all the granulations was found to be less than 2%. On the other hand formulations of Trial 7 to Trial 10 were prepared which act as a immediate released layer. Preformulation parameters of these granulations were also evaluated and found to be satisfactory (Table 3).

The granules containing sustained release part were compressed first to obtain a tablet. To these yellow colored Atorvastatin calcium granules were poured into the die cavity and compressed again resulting in a bilayered tablet containing an immediate release layer of Atorvastatin calcium and sustained release layer of Metformin hydrochloride. The tablets were subjected for weight variation, hardness, thickness and friability and drug content. These parameters were found to be within standard limits and satisfactory (Table 4). The bi-layered tablet was further subjected for *in vitro* dissolution studies as described earlier to ascertain the release pattern. Among the formulations prepared for sustain release Trial 6 was found to be acceptable. Hence the formulation was tested for reproducibility and the same formulation was used in combination with various formulations (Trial 7 to Trial 10). The release profiles Trial 10 showed better results to that of innovator.

These release profiles of Metformin hydrochloride and Atorvastatin calcium complied with standards and specifications of USP (Fig.2 and Fig.4). The percentage drug release of bi-layer tablets in Trial 10 when compare with Metformin innovator was found to be between 42 to 102%. The percentage drug release of bi-layer tablets of Trial 10 when compare with Atorvastatin innovator was found to be between 92 to 96%. The optimized formula was checked for reproducibility. Among the formulations Trial 10 containing Atorvastatin calcium 10mg and Metformin hydrochloride 500mg per tablet is similar and equal to the innovator product in respect of all tablet properties and dissolution rate and showed good hardness, thickness and low friability. The percentage drug release for this formulation showed the better drug release 96% of Atorvastatin calcium in 45 minutes as immediate release drug and 102% of Metformin hydrochloride in 12 hrs as sustain release tablet.

CONCLUSION

Optimized immediate release layer of Atorvastatin calcium and sustained release layer of Metformin hydrochloride showed satisfactory pre and post compression parameters. Formulation Trial 10 is considered to be the best with the desired drug release. The polymers which have been used in the best formulation are HPMC K100M CR. Bi-layer tablet is suitable for treatment of NIDDM and Hyperlipidemia by sequential release of the drug. It was concluded that Atorvastatin and Metformin hydrochloride Bi-layer tablets can be prepared successfully. Hence the bi-layered tablet designed to possesses all the qualities of a formulation. But feasibility of the production in large scale must be explored.

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