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Research Article

FORMULATION AND *IN-VITRO* EVALUATION OF NICARDIPINE HYDROCHLORIDE BILAYERED TABLET FOR CONTROLLED RELEASE

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ABSTRACT
The aim of present research work was to prepare and evaluate the controlled release bilayered tablet of Nicardipine HCL to improve its bioavailability for the treatment of hypertension. To minimize critical process parameters, two layer compression method was used for the formulation of Bilayered tablets. The appropriate formulation was achieved successfully with the combination of Polymers MCC, Carbopol 71G and HPMC K100M produced desired release profile for Metoprolol succinate extended release layer. The combination of disintegrating agents that is Sodium starch glycolate and Dicalcium phosphate produced desired release rate for Nicardipine immediate release layer. The results reveal that formulation F7 has met the objective of controlled drug release for over a period of 12 hrs. The formulation F7 ascertained the efficacy of the controlled released Bilayered tablet of Nicardipine and Metoprolol ER tablet in hypertension. This sustained release Bilayered tablet with the combination of Nicardipine and metoprolol can be used in the management of different types of hypertension. The formulation F7 of combination of Nicardipine and metoprolol showed controlled release profile among the other, Hence it was considered as an optimized formulation.

Keywords: Sustained Release, Bilayered Tablet, Hypertension etc.

1. INTRODUCTION
Hypertension is a major, worldwide health problem owing to its high prevalence and association with increased morbidity and mortality [1]. Hypertension is a key risk factor for cardiovascular morbidity and mortality and approximately 7.1 million deaths per year can be directly attributed to poor control of blood pressure [2]. Hypertension is also a major risk factor for stroke (Ischaemic and Haemorrhagic), myocardial infarction, heart failure, chronic kidney disease, peripheral vascular disease, cognitive decline and premature death [3].
Hypertension is classified as either primary (essential) hypertension or secondary hypertension; about 90-95% of cases are categorized as "primary hypertension" which means high blood pressure with no obvious underlying medical cause [4]. The remaining 5-10% of cases (secondary hypertension) caused by other conditions that affect the kidneys, arteries, heart or endocrine system [5].
Bilayer tablet is new era for the successful development of controlled release formulation along with various features to provide a way of successful drug delivery system [6]. Bi-layer tablets can be primary option to avoid chemical incompatibilities between APIs by physical separation and to enable the development of different drug release profiles [7].

2. MATERIAL AND METHODS
Nicardipine HCL and Metoprolol Succinate was gift sample from Elder Pharmaceutical Ltd, Dehradun. All other ingredients used in the formulation are taken from college laboratory. All chemical and reagents were of analytical grade.

2.1. Preparation of Bilayered Tablets [8]
In order to prepare bilayered tablets, fast-release Nicardipine and extended-release Metoprolol single-layer tablet formulations were initially prepared to gain insight into the dissolution profile of each layer separately with the aim of selecting the best formulations of each that could be combined together to provide bilayer tablets with suitable release pattern characterized by initial fast-release of Nicardipine and extended-release of Metoprolol for 12 hrs in 0.1N HCl. The drug and

polymers for both immediate release and extended release layers were passed through a sieve # 80 before their use in the formulation.

2.2. Formulation of the Fast-Release Layer of Nicardipine [9]

The composition of the fast-release tablet formulation of NC is shown in Table 1. Nicardipine Hydrochloride (NC) was selected, based on its superior dissolution properties in 0.1N HCl, to be incorporated into fast-release layer of NC of bilayered tablets. Dicalcium phosphate and sodium starch glycolate were added in different ratios as tablets diluents and superdisintegrant, respectively. They were mixed thoroughly with the NC in a mortar with the help of pestle for 30min. Then, talc and magnesium stearate were added as glidant and lubricant, respectively, to the powder blend and mixed for an additional 5min. The resultant powder blend was compressed under constant pressure using a single punch tablet machine (Kilburns, Allahabad, India) into 120mg tablets, each containing a total of 40mg NC.

2.3. Formulation of the Extended-Release Layer of Metoprolol [10]

The detailed composition of single-layer extended-release tablet formulation of MTS is presented in Table 2. Each ingredient was sifted through #30 sieves. The specified quantity (50mg) of MTS was mixed with different ratios of MCC, HPMC and Carbomer 71G in glass mortar with the help of pestle for 30min. The PVPK-30 binder solution was added slowly into this mixture. The wet mass was passed through sieve with 7mm screen. The wet mass was dried at 55-60°C until LOD was not more than 3.5%. The dried material was sifted through #20 sieves. Then, magnesium stearate were added to the dried blend and mixed for additional 5min. The powdered blend was compressed under constant pressure using a single-punch tablet machine into 140mg tablets, each containing 50mg of MTS.

2.4. Formulation of Nicardipine Fast-Release and Metoprolol Extended-Release Bilayer Tablets [11,12]

Tables 1 and 2 provide the detailed composition of NC fast-release layer and MTS extended release layer for the formulation of bilayer tablets. The bilayer tablets were prepared by direct compression using a single-punch tablet machine where its die was initially filled with the weighed amount of sustained release fraction and lightly compressed, and then the fast-release portion was added directly onto the obtained compressed tablet, and then recompressed together at 7-8 kg/cm^2 to combine them. It was found that, at the compression force of 7-8 kg/cm^2, there was no layer separation among the two layers of bilayered tablets. The total weight of each bilayered tablet was adjusted to 260mg, containing 20 mg of NC in fast release layer and 50mg of MTS in extended-release layer.

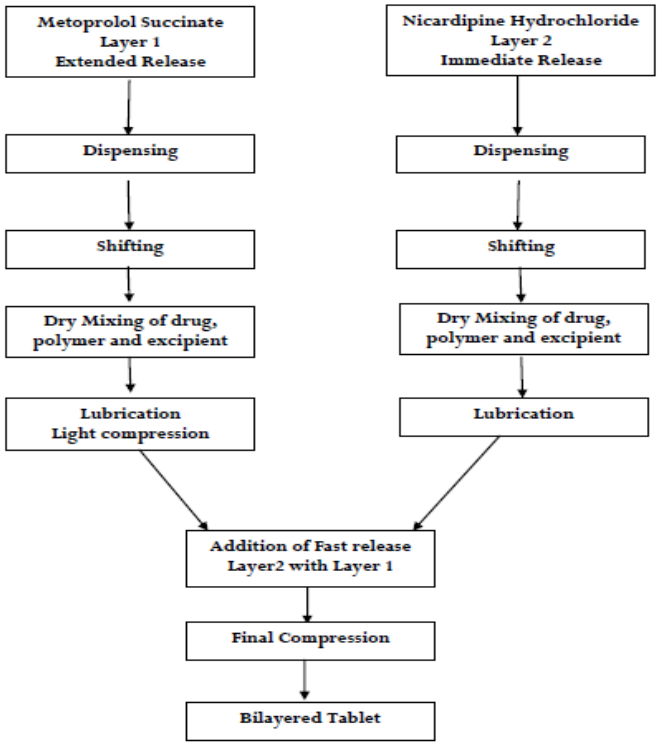

Fig 1: Flow Chart of Bilayered Tablet Formulation

3. RESULT AND DISCUSSION

Various formulations of bilayered tablets were developed, using MCC, carbopol 71G, HPMC K100M as polymers and PVP K30 as binder for extended release layer and Sodium starch glycollate as disintegrating agents and Dicalcium phosphate as diluents for immediate release layer. The bilayer tablets were prepared by compressing the individual layers together in a single punch tablet machine. The bilayer tablets were prepared were subjected to tablet properties like thickness, hardness, friability, weight variation and *In-vitro* drug release study [13].

Thickness of formulation no. F1 to F8 are in the range of 3.82 to 3.96mm respectively.

The average hardness of all the compressed tablet; formulation no. F1 to F8, lies in the range of 8 to 9 kg/cm^2.

The average friability of all the formulation no. F1 to F8 lies in the range of 0.11 to 0.22%.

Average weight of all Bilayered tablets was found to be around 260 mg (±5%). Thus all the formulations were found to be complying with the standards given in IP.

The *in vitro* drug release profile of Nicardipine from bilayer tablet containing different proportion of sodium starch glycolate and Dicalcium phosphate are shown in figure 2. It was shown that as the amount of sodium starch glycolate increases in formulation the drug release was increased [14]. The *in vitro* drug release profile of Metoprolol from bilayered tablet containing different proportions of MCC, Carbopol 71G and HPMC K100M are shown in fig. 3. The dissolution studies were carried out up to 24 hours using 0.1N HCl as dissolution medium.

All the batches of the fabricated tablets were of good quality with regard to hardness, friability and weight variation. The results of dissolution studies of various formulations were described that the vitro drug release of the entire formulations F7 has satisfied drug release for the extended period of 12 hrs. The release of drug depends not only the nature of the matrix but also depends upon the drug polymer ratio [15].

Table 1: Composition of Nicardipine fast release layer

Ingredients (mg)	Formulation code							
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
Nicardipine HCL	40	40	40	40	**40**	40	40	40
Sodium starch glycolate	3.0	3.5	4.0	4.5	**5.0**	5.5	6.0	6.5
Dicalcium phosphate	q.s.	q.s.	q.s.	q.s.	**q.s.**	q.s.	q.s.	q.s.
Magnesium stearate	1.0	1.2	1.4	1.4	**1.6**	1.6	1.8	2.0
Talc	6.0	5.8	5.6	5.6	**5.4**	5.4	5.2	5.0
Total Tablet weight	120	120	120	120	**120**	120	120	120

Table 2: Composition of Metoprolol Succinate extended release layer

Ingredients (mg)	Formulation code							
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
Metoprolol Succinate	50	50	50	50	50	50	**50**	50
MCC	25	20	27	25	25	23	**20**	20
HPMC K100M	45	35	25	23	25	25	**27**	30
Carbomer 71G	--	15	10	12	15	12	**15**	12
PVP K30	15	15	20	20	20	20	**20**	20
Isopropyl alcohol	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	**q.s.**	q.s.
Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5	**2.5**	2.5
Total Tablet weight	140	140	140	140	140	140	**140**	140

Table 3: Post- compression studies of Bilayered Tablet

Parameter	**Unit**	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
Thickness	Mm	3.92	3.84	3.94	3.88	3.82	3.96	3.85	3.90
Hardness	Kg/cm^2	8	8.5	8.5	9	8.5	8.5	8	8
Friability	%	0.12	0.14	0.22	0.20	0.11	0.14	0.12	0.16
Uniformity of weight	Mg	260	264	258	265	264	262	262	264

Table 4: *In vitro* release profile of Nicardipine from Fast-release tablets

Time (min)	Cumulative % drug release (F7)
10	20±1.8%
20	32±2.6%
30	68±3.8%
40	83±4.2%
60	98±2.4%

Value represent mean ± SD (n=3)

Table 5: *In vitro* release profile of Metoprolol from Extended-release tablets

Time (hrs)	Cumulative % drug release (F7)
1	14±1.6%
2	25±2.8%
4	38±3.2%
8	63±4.6%
12	88±3.8%

Value represent mean ± SD (n=3)

Table 6: *In vitro* release profile of Nicardipine from the prepared Bilayered tablets

Time (min)	Cumulative % drug release (F7)
10	18±1.6%
20	30±2.4%
30	56±3.8%
60	89±4.6%
120	98±2.4%

Value represent mean ± SD (n=3)

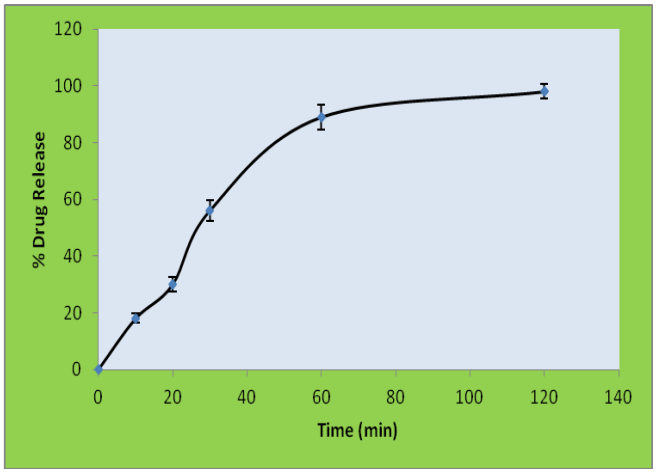

Fig. 2: Cumulative % Nicardipine release from the prepared Bilayered tablets

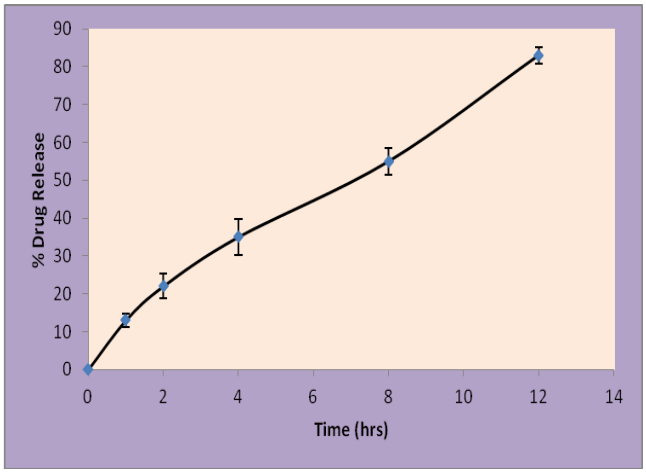

Fig. 3: Cumulative % Metoprolol release from the prepared Bilayered tablets

4. CONCLUSION

The present work involves the formulation development, optimization and in-vitro evaluation of bilayered matrix tablets of Nicardipine HCl and Metoprolol succinate, with fixed dose Metoprolol succinate forming the extended release layer and Nicardipine HCl immediate release layers for the treatment of hypertension. To minimize critical process parameters two layer compression method was selected for the formulation of Bilayered layer tablets.

The final suitable formulation was achieved fruitfully with the combination of Polymers that is MCC, Carbopol 71G and HPMC K100M produced desired release profile for Metoprolol succinate extended release layer. The combination of disintegrating agents that is Sodium starch glycolate and Dicalcium phosphate produced desired release rate for Nicardipine immediate release layer. The results reveal that formulation F7 has met the objective of extended drug release for over a period of 12 hrs.

This multi-centric study demonstrated the efficacy of the Bilayered tablet of Nicardipine and Metoprolol ER tablet in essential hypertension. Since the Bilayered tablet have shown to be efficacious with good release profile, this Bilayered tablet with the combination of Nicardipine and metoprolol can be used in the management of mild to moderate hypertension.

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Conflicts of interests

The authors have No conflict of interest.

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