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FORMULATION AND EVALUATION OF BILAYER TABLET OF METOPROLOL SUCCINATE AS A CONTROLLED RELEASE AND AMLODIPINE AS A IMMEDIATE RELEASE

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ABSTRACT:
The objective of present work is to develop double layer tablet of Amlodipine as immediate and Metoprolol succinate as controlled release tablet by using HPMC as a release controlling agent. Medium and high viscosity grade used to prepare Matrix tablet. The tablets prepared by wet granulation method, well subjected to physical characterization and *invitro* drug release studies. The *invitro* drug release was carried out using USP apparatus at 50rpm in 500ml of Phosphate buffer medium (pH 6.2). The drug release rate was strongly influenced by the type of polymers and the concentration of polymer. The drug release of HPMC, Ethyl cellulose and drug release was inversely correlated. To analyze the release mechanism, Kosmeyer and Pepaas equation, Higuchi, first order model were used.

Keywords: Metoprolol succinate, Amlodipine, Controlled release, Tablet.

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INTRODUCTION

Hydrophilic polymers like HPMC have been considerable attention in the formulation of controlled release drug delivery system for various drugs. HPMC, a semisynthetic derivative of cellulose, is popular as a swellable and hydrophilic polymer. Its non toxic nature and ease of handling makes it an excellent release retardant material. On exposure to aqueous fluids, the polymer in tablet hydrates to form a viscous gel layer, through which the drug is released by diffusion and/ or erosion of the matrix. The formulation factors influencing the drug release from hydrophilic matrices are polymer viscosity, polymer particle size, drug loading, compression force, tablet shape, formulation excipient and processing technique[1-4]. The dissolution can be either disentanglement or diffusion controlled, depending on the polymer molecular weight and the thickness of the diffusion boundary layer[5].

Systemic hypertension represents a significant risk factor for the development of atherosclerotic coronary artery disease and myocardial infarction, cerebrovascular accidents and congestive heart failure. A major barrier to the management of hypertension is the extent to which patients comply with the treatment regimen.

Metoprolol succinate is a β–1–selective adrenoceptor blocking agent. Its chemical name is (I)- (Isopropyl amino)-3-{P-(2 methoxy ethyl) phenoxyl}-2-propanol succinate site in the body to achieve promptly and maintain the desired drug concentration[6,7]. Animal and human experiments indicate that metoprolol slows the sinus rate and decrease AV nodal conduction. Metoprolol succinate has a lower peak plasma concentration and higher trough plasma levels than Metoprolol tartrate[8].

(RESEARCH ARTICLE)

Amlodipine a long acting calcium channel blocker. It inhibits calcium ion influx across cell membranes selectivity, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Negative inotropic effect can be detected *invitro* but such effects have not been seen in intact animals at therapeutic doses. Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in BP.

MATERIAL AND METHODS

Metoprolol succinate (Astra Zeneca Pharma India Ltd., Amlodipine (Cadila Health care Ltd.,), HPMC (Signet chemical corporate), Ethyl cellulose (Hercules), IPA (Sherf Eastern Chemical).

Preparation of tablets

Wet granulation was used for the preparation of controlled release formulation of Metoprolol succinate. The weighed quantity of drug and excipients were passed through appropriate sieves. This involves the exclusion of gritty particles from finer ones as former may result in irregular surfaced granules. This shifting was done by using sieve #40. Granulation fluid was prepared by homogenously mixing the binder with granulating solvent. IPA was used as a granulating solvent. Blending the drug and excipients was carried out by mixing. The granulation fluid was added slowly until wet mass like substance was formed. The granular mass was passed through sieve #12 and kept for drying. The granules were spread on a tray dryer and dried at 50^0C. Drying was continued until desired L.O. D was obtained. The dried granules were lubricated, using suitable lubricant after passing through sieve#20.

Table no.1, Composition of the first layer containing Metoprolol succin

Ingredients	N2 (gm)	N3 (gm)	N4 (gm)	N5 (gm)	N6 (gm)
Metoprolol Succinate	23.8	23.8	23.8	23.8	23.8
Aluminium silicate	-	10	15	15	15
HPMC (K4)	50	55	55.5	55.5	50
E 50V	15	20	20	20	20
Lactose	22.5	22.5	20	20	20
HPMC 1L	75	100	102	105	108
Ethyl Cellulose	15	20	20	20	20
SSF	2	2	2	2	2

The granules were compressed by 16 stationary RIMEC compression machine using 8mm concave punches. The Metoprolol succinate granules (MS, Controlled release) and Amlodipine besylate (AB, immediate release) are compressed and make as double layer tablet. Formula for five formulations was given in Table No. 1 and Table No. 2.

Table No: 2, Composition of the second layer containing Amlodipine.

Ingredients	N2 (gm)	N3 (gm)	N4 (gm)	N5 (gm)	N6 (gm)
Amlodipine	5	5	5	5	5
MCC 102	60	65	75	75	75
DCP	40	40	40	40	40
SSG (Granulation)	20	20	20	20	20
SSG (Lubrication)	5	5	5	5	5
Magnesium stearate	1	1	1	1	1
PVPK30	10	10	10	10	10

Physical Characterization

Formulations were subjected to various pharmacopeial (weight variation, Friability, DT, Assay, Hardness) tests in order to qualify for the dissolution studies. Assay was performed as per the method developed. Physical Characterization studies are reported in Table No: 3.

Table No:3, Physical Characters of the tablet

Physical Characters	N2 (gm)	N3 (gm)	N4 (gm)	N5 (gm)	N6 (gm)
Friability (%)	0.635	0.697	0.665	0.654	0.642
Hardness (kg/cm2)	3.5	4.5	4.5	5.0	5.0
Swelling Index (%)	7.0	7.003	7.021	7.001	7.003

Drug release study: The dissolution profile of the solid dispersion was determined using a six panel USPXXIII dissolution apparatus taking 500ml of Phosphate buffer pH 6.8 solution for 20 hours. The dissolution medium was maintained at a temperature of 37 ± 1^0C. The speed of paddle was 50rpm. The samples were withdrawn at 1st, 4th, 8th & 20th hour. The samples were filtered and the absorbance were determined at 286nm (MS) and 237 nm (AB) by using HPLC Agilent 1100 series, column Zorbax xdb C8, Injection volume 50µl and flow rate 1.0ml/min. Change in wavelength from 280nm to 237nm after the elution of Metoprolol succinate peak (Approximately after 4 min.). The percentage of drug release is shown in fig.No:1 and Table No. 4. The prepared mobile phase was filtered through 0.45µm micro pre filter and degassed by sonication for 10 minutes[9,10].

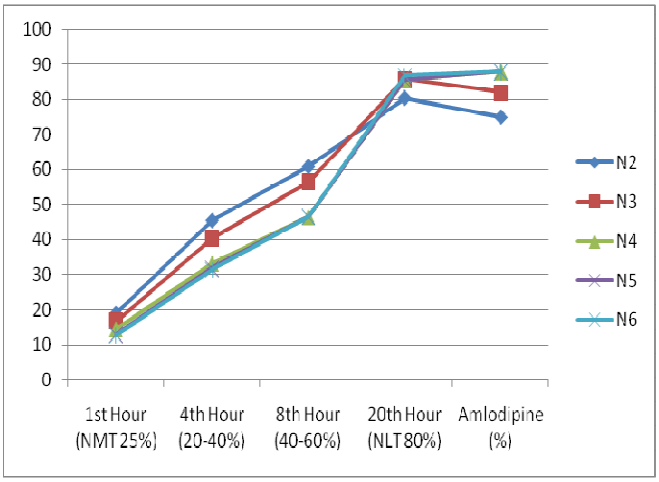
TableNo: 4. Comparative dissolution profile of Metoprolol succinate & Amlodipine bilayer tablet.

Dissolution rate	N2	N3	N4	N5	N6
1st Hour (NMT 25%)	18.85	16.68	14.5	13.0	12.7
4th Hour (20-40%)	45.5	40.4	33.3	31.9	31.4
8th Hour (40-60%)	60.9	56.6	47.5	46.6	46.6
20th Hour (NLT 80%)	80.5	85.9	86.5	85.5	86.9
Amlodipine (%)	75	82	88.6	88	88

RESULTS AND DISCUSSION

Various pharmaceuticals test indicated the good quality of the selected formulations with respect to friability, hardness, swelling index. As per USP[11], the powder blend of all the batches exhibited excellent flow. A weight variation was found less than 0.1%. The first layer (MS) of the tablets are circular, concave surface tablets which is white in colour and the second layer

(AB) are circular concave which is light pink in colour, the granules are fine with in range of 15-20% which is ideally suited for the best flow in the hopper so as to minimize the weight variation which will lead to uniformity in drug content. The formulation containing HPMC and Ethyl cellulose were formulated using the data available in the literature by trial and error method. In the case of matrix embedded controlled release tablet formulations of Metoprolol succinate using HPMC and Ethyl cellulose in combination as the retarding polymers. In the dissolution medium, the tablet was found to swell and burst out the drug. This result could be attributed to the presence of HPMC, which rapidly takes up the water molecules leading to swelling. Incorporation of ethyl cellulose was to control the drug release to some extent, which could be attributed to the decreased penetration of the solvent molecules in the presence of hydrophobic polymer leading to decreased diffusion of the drug form the matrix.



Invitro dissolution drug release profile

The *invitro* dissolution profile of the optimized formulation showed the release profile was according to the predetermined manner. The drug release rate is significantly dependent on the proportion and type of polymer used[12]. Fitting of the release data to the korsmeyer and pepaas equation found that the release rate at 20th hour for the optimized was found to be 30.8 ± 2.519, and the diffusion coefficient was calculated to be 0.4803±0.04041. This however appears to indicate that the optimized formulation is a coupling of diffusion and erosion mechanism which is called as anomalous diffusion, because in this formulation the hydrophilic nature causes erosion, creating pores in the matrix whereas hydrophobic nature causes diffusion. From the first order plot the regression values was found to be 0.9948, which predicts that the release profile follows the first order reaction. The method was very specific and there was no interference of the excipients or impurities with the principle peak. For the five formulations N2 to N6, the release pattern was studies, in these formulation N6 was optimized where the percentage of drug release and assay are within the limit at 1st, 4th, 8th & 20th hour.

CONCLUSION

The matrix bilayered tablets of Metoprolol succinae as controlled release and amlodipine as immediate release were prepared by wet granulation method. Formulation from N2 to N6 release pattern was studied and N6 was considered to be the best with the desired drug release. The polymers used in the formulation are HPMC (K4), HPMC 1K, PVPK, E 50V, Ethyl Cellulose. This formulation has also shown the required release pattern and complies with USP specification. Hence the bi-layered tablet designed possesses all the qualities of controlled release and immediate release formulation.

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