



Formulation development and evaluation of metoprolol succinate sustained release and hydrochlorothiazide immediate release bilayer tablet

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ABSTRACT

Bilayer tablet concept has been investigated to develop combination of sustained and immediate release formulations. The present study aims to develop and evaluate to provide a combined therapy through a single tablet in which combinations of Metoprolol succinate and Hydrochlorothiazide were used. The pharmacokinetics advantage of this formulation was, drug release from the fast releasing layer leads to immediate rise in the blood concentration. But the drug concentration in the blood is maintained at steady state level as the drug is released from sustained released layer. Dose is varied depends upon the patients severity conditions. It varied from metoprolol succinate 25 mg to 200 mg and hydrochlorothiazide 12.5 mg to 25 mg. Bilayer dosage form containing Metoprolol succinate SR and Hydrochlorothiazide IR respectively for the management of hypertension.

Keywords: Bilayer; metoprolol succinate; Hydrochlorothiazide; Hypertension

INTRODUCTION

The treatment of acute disease or a chronic illness has been mostly accomplished by delivery of drugs to patients using various pharmaceutical dosage forms including tablets, capsules, pills, suppositories, creams, ointments, liquids, aerosols, and injectable as drug carrier[1]. The oral route of administration has been used for both conventional and novel drug delivery systems. Recently several technical advancements resulted in the development of new techniques for drug delivery. These techniques are capable of controlling the rate of drug release, extending the duration of therapeutic activity and targeting of drug to the needed area [2]. To achieve the goal, the dosing frequency may be minimized once or at most twice daily. An approximately designed extended release dosage form (e.g.) sustained drug delivery system can be a major advance in this direction [3]. Drugs may be administered by variety of routes but oral administration is adopted wherever possible. There are many applications and large markets for non-oral products and the technologies that deliver them (on drug delivery). Oral delivery of drugs is the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in formulations. Amongst drugs that are administered orally solid oral dosage forms i.e. tablets and capsules, represent the preferred class of products. Out of the two oral solid dosage forms, the tablets have number of advantages like tamper proof, low cost and speed of manufacturing (direct compression), ease of administration, patient compliance and flexibility in formulation. The basic goal of therapy is to achieve a steady –state blood or tissue level that is therapeutically effective and non-toxic for extended period of time [4].

EXPERIMENTAL SECTION

Formulation of Metoprolol succinate granules (Layer 1)

Different formulations (F1-F7) were prepared with hydroxyl propyl methyl cellulose of different grades like HPMC-K₄M, HPMC-K₁₀₀, HPC Polymers and other excipients. The granules were prepared by wet granulation technique. Metoprolol succinate, HPMC K₄, HPMC K₁₀₀, microcrystalline cellulose were sifted through # 30 mesh. The

sifted blend was allowed to mix thoroughly in rapid mixer granulator for 15 minutes at slow speed of 300 rpm. The binder solution was prepared by mixing IPA and PVP k30. The prepared binder solution was added slowly to the powder blend and mixed uniformly. The wet mass was passed through sieve No 20 to get the granules. The granules were dried in the FBD by using the slow blower. The semi dried granules were sifted through 20 meshes and the granules were collected. The above sifted blend was dried and the granules were milled at 1.5 mm screen using knives. The above sifted and milled granules were dried at 65°C (inlet temperature) and 45°C (outlet temperature) in FBD until the LOD (loss on drying) of granules was reached limit between 2-4% w/w. The sifted HPMC-K₄M, HPMC-K₁₀₀, HPC, and purified talc were mixed with dried granules at 15 minutes. Final blend was collected.

Formulation of Hydrochlorothiazide granules (Layer 2)

Different formulations (F1-F6) were prepared with Lactose, microcrystalline cellulose, maize starch, colloidal silicon dioxide and other excipients. The granules were prepared by wet granulation technique. Lactose, microcrystalline cellulose, maize star, colloidal silicon dioxide were sifted through # 30 mesh and brilliant blue were sifted through 100 #mesh. The sifted blend was allowed to mix thoroughly in rapid mixer granulator for 15 minutes at slow speed 300 rpm. The binder solution was prepared by mixing acetone and hydrochlorothiazide. The binder solution was added slowly to the powder blend and mixed uniformly. The wet mass was passed through sieve no 20 to get the granules. The granules were dried in the FBD by using the slow blower. The semi dried granules were sifted through 20 mesh and the granules were collected. The sifted blend was dried and the granules were milled at 1.5 mm screen using knives. The above sifted and milled granules were dried at 65°C (inlet temperature) and 45°C (outlet temperature) in FBD until the LOD (loss on drying) of granules was reached limit between 2-4% w/w. Magnesium stearates were mixed with dried granules at 5 minutes and final blend was collected.

Preparation of bilayer tablets

Bilayer tablet punching machine consists of two hoppers and two feed frames separately without intermixing first and second layer of granules as shown in figure 1. Initially the die cavity was adjusted for proper die cavity filling and pressure adjustment was made to get proper hardness of tablet. Now granules are ready for compression of bilayer tablet.

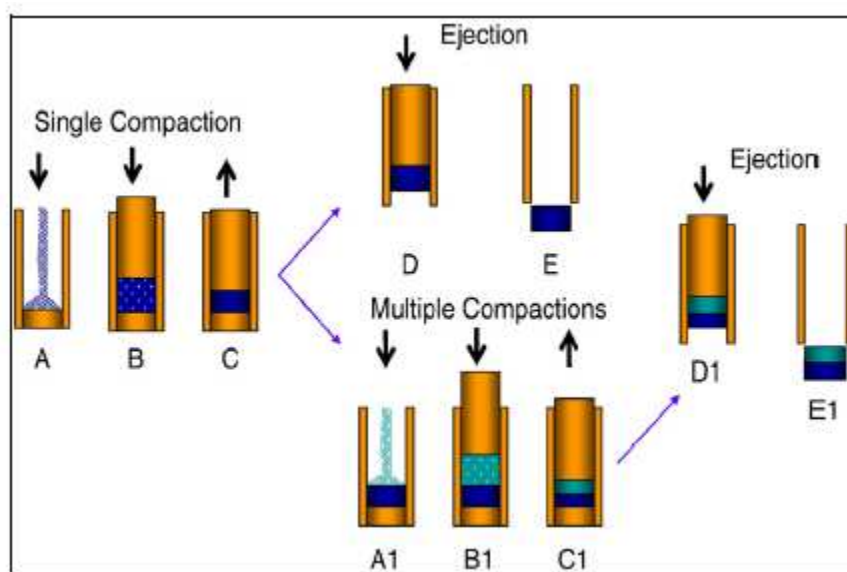
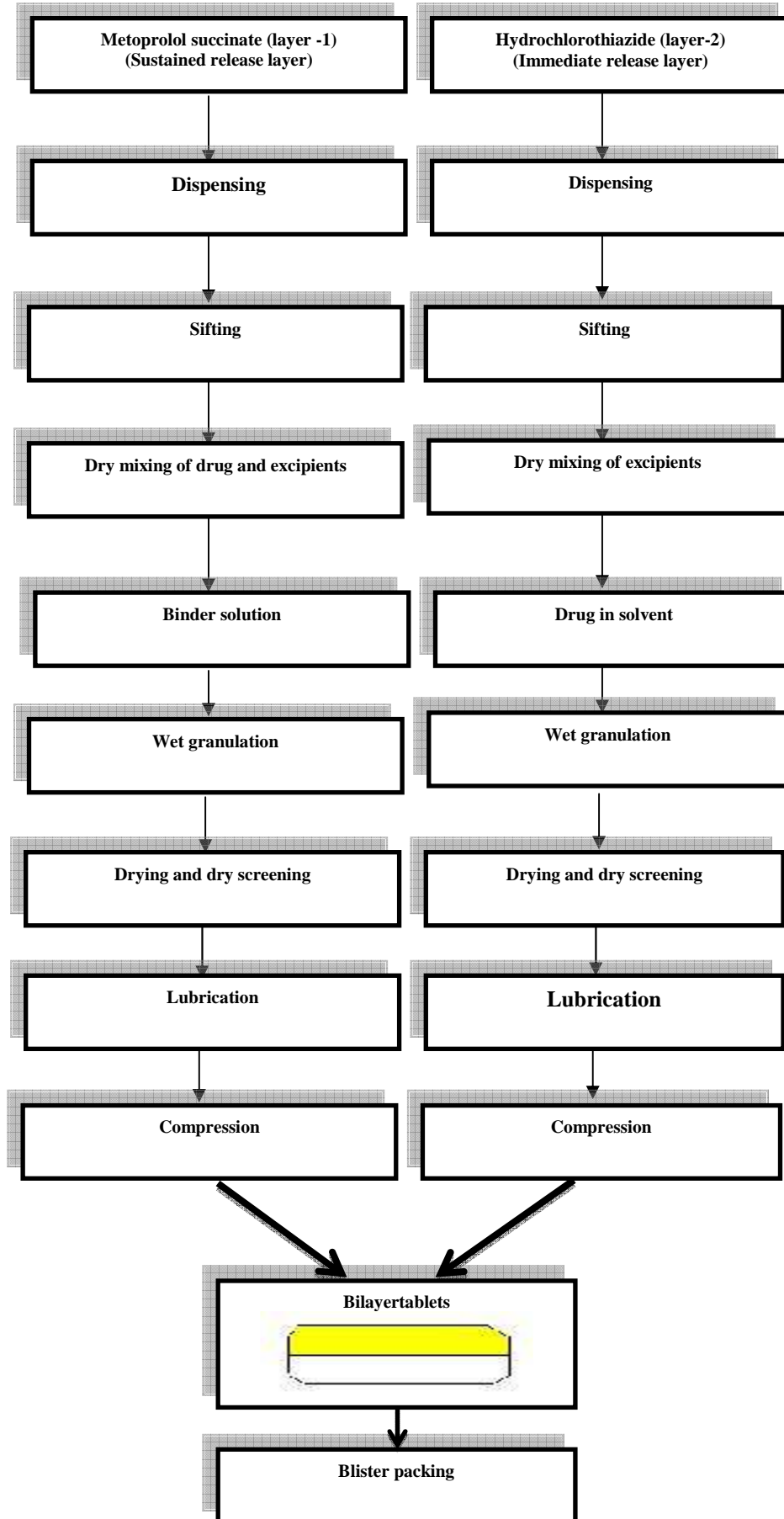


Figure 1. Bilayer Tablet Preparation using Punching Machine

Metoprolol succinate granules (layer1) were taken in one hopper and hydrochlorothiazide was taken in another hopper. Metoprolol succinate layer blend is initially pre-compressed with low hardness and hydrochlorothiazide layer blend is compressed over it, till the desired hardness is achieved. This technology is called Bi-layered technology [5]. Second layer was differentiated by colored granulation. The evaluated granules were compressed using cadmech 27 station automatic compressing machine with a 13/ 32 inch, standard circular shape with plain surface punch's and dies with compressing force 4.5 don.

Bilayer Process Flow Chart



Evaluation of bilayer tablets of Metoprolol succinate and Hydrochlorothiazide**General appearance**

The general appearance of tablets, its visual identity and overall elegance is essential for consumer acceptance. The control of general appearance involves measurements of tablets size, shape, colour, presence or absence of odour, taste, physical flows and consistency [6,7].

Hardness test

The hardness of tablets (kg/cm^2) was carried out by using Monsanto type hardness tester. The tablet was placed horizontally in contact with the lower plunger of the Monsanto hardness tester and zero reading was adjusted. Then the tablet was compressed by forcing the upper plunger until the tablets breaks and this force was reported.

Friability test

Friability is the loss of weight of tablet in the container/ package due to removal of fine particles from the surface. It usually measured by roche friabilator. The drum is attached to the horizontal axis of a device that rotates at 25 ± 1 rpm. It should be ensured that with every turn of the drum the tablets roll or slide and fall on to the drum wall. Ten tablets are weighed initially (w_1) and placed in the apparatus where they are exposed to rolling. After 100 revolutions, the tablets are weighed (w_2) and this was compared with the initial weight of the tablet. The value is expressed in percentage. A maximum loss of weight not greater than 1% acceptable for most of tablets. The friability was determined using the following formula

$$\text{Friability} = \frac{(W_1 - W_2)}{W_1} \times 100$$

Where, W_1 = Weight of ten tablets before test

W_2 = Weight of ten tablets after test.

Weight variation test

Twenty tablets of each formulation were selected at random and weighed individually. The weight of individual tablet was noted. Average weight was calculated from the total weight of the tablets. The individual weight was compared with average weight. The weight of not more than two tablets should not deviate from the average weight. It was compared with the percentage given in the standard table. The percentage deviation was calculated by using the formula

$$\text{Percentage deviation} = \frac{\text{Individual weight} - \text{Average weight}}{\text{Average weight}} \times 100$$

Uniformity of weight and percentage deviation

S. No	Average weight of tablet	Percentage deviation
1	80 mg or less	± 10.0
2	More than 80 mg but less than 250 mg	± 7.5
3	250 mg or more	± 5.0

Thickness of tablets

The thickness of all tablets was determined by using vernier caliper. Six tablets from each formulation were used and average values were reported [8].

IR Spectral analysis

It is used to determine the interaction between the drug polymer and excipients. The drug and polymer must be compatible with one another to produce a product stable, efficacious and safe. The KBR disc method was used for preparation of sample and spectra were recorded over the wave number 4000 to 500cm^{-1} in a SHIMADZU FTIR spectrophotometer. The IR spectral analysis for drug and polymer was carried out. If there is no change in peaks of mixture when compared to pure drug, it indicates the absence of interactions [9].

RESULTS AND DISCUSSION**Post Compression Parameters of Metoprolol Succinate and Hydrochlorothiazide Bilayer Tablet**

All the patches were evaluated for organoleptic properties, weight variation, thickness, Hardness, Friability test, Drug content are evaluated and those values are listed in Table 1.

Organoleptic properties

The formulated tablets from formulations F2 to F7 were evaluated for their organoleptic characters. The tablets were circular shaped and layer 1 was white and layer II was blue colour. All the tablets show elegance appearance.

Weight variation

From the results of weight variation it was found that the formulated trial batch F2 to F7 were the results found that range between 374.70 ± 3.25 to 377.00 ± 1.15 mg. It was proved that the IP limit and complies the test. The accepted percentage deviation of tablet was $\pm 5\%$ for more than 250 mg tablet weight.

Thickness

From the results of thickness it was found that the formulated trial batch F2 to F7 were the results found that range between 4.71 ± 0.1 to 4.85 ± 0.2 mm. It was proved that the in house specifications and complies the test.

Hardness

From the results of hardness it was found that the formulated trial batch F2 to F7 were the results found that range between 4.85 ± 0.25 to 5.36 ± 0.22 kg/cm². It was proved that the in house specifications and complies the test.

Friability test

From the results of friability it was found that the formulated trial batch F2 to F7 were the results found that range between 0.26 ± 0.06 % to 0.79 ± 0.03 % respectively. It was proved that the in house specifications and complies the test.

Drug content

From the results obtained from the formulations F2 to F7 the maximum and minimum range was in metoprolol succinate 98.91 ± 1.67 to 103.32 ± 1.24 % and hydrochlorothiazide was 92.47 ± 0.32 to 107.15 ± 1.36 % using HPLC method. The drug content of metoprolol succinate equivalent to metoprolol tartrate and hydrochlorothiazide tablet range between 90.0 % to 110.0% limit described in the USP. It was matched in USP mentioned limit. From the results it was found that the formulation trial batch F1 we found that the coherent mass was obtained without the addition of IPA.

Table 1 Evaluations of Bilayer Tablets of Metoprolol Succinate Sustained Release and Hydrochlorothiazide Immediate Release

S.NO	PARAMETERS	Specification	F1	F2	F3	F4	F5	F6	F7
1	Description	Blue / white coloured circular shaped uncoated bilayer tablet	-	Complies with the internal specification	Complies with the internal specification	Complies with the internal specification	Complies with the internal specification	Complies with the internal specification	Complies with the internal specification
1	Weight variation (mg)	$375 \text{ mg} \pm 5\%$	-	375.2 ± 2.50	376 ± 1.73	374.70 ± 3.25	377.00 ± 1.15	376.5 ± 4.06	375.20 ± 2.23
2	Thickness (mm)	$4.8 \text{ mm} \pm 0.2$	-	4.71 ± 0.1	4.70 ± 0.08	4.85 ± 0.07	4.85 ± 0.2	4.76 ± 0.1	4.85 ± 0.1
3	Hardness kg/cm ²	NLT 3.0	-	4.85 ± 0.25	5.01 ± 0.27	5.03 ± 0.29	5.30 ± 0.19	5.36 ± 0.22	5.10 ± 0.28
4	Friability (%)	NMT 1%	-	0.26 ± 0.06	0.52 ± 0.05	0.53 ± 0.05	0.78 ± 0.03	0.79 ± 0.03	0.53 ± 0.05
5	Drug content								
	a) Metoprolol succinate equ.to Metoprolol tartrate	90- 110%	-	98.91 ± 1.67	99.93 ± 1.41	100.02 ± 0.96	102.37 ± 1.22	101.18 ± 1.02	103.32 ± 1.24
	b) Hydrochlorothiazide	90 – 110%		92.47 ± 0.32	104.25 ± 0.69	98.09 ± 0.25	101.09 ± 0.40	107.15 ± 1.36	107.15 ± 1.36

All the values are mean \pm SD (n=3)

FTIR Spectral Analysis

The FTIR studies of pure Metoprolol succinate, Hydrochlorothiazide, HPMC K4, HPMC K100, HPC, Metoprolol succinate + HPMC K4, Metoprolol succinate + HPMC K100, Metoprolol succinate + HPC, Metoprolol succinate + HPMC K4 + HPMC K100 + HPC and formulations of Metoprolol succinate and Hydrochlorothiazide Bilayer tablet were carried out to study the interaction between the drug and polymer.

IR spectral analysis showed that the fundamental peaks and patterns of the spectra were similar both in pure drugs, polymers and with formulation of bilayer tablet. This indicated that there was no chemical interaction or decomposition of Metoprolol succinate and Hydrochlorothiazide in the presence of polymers [10]. The results were showed in Figure 2.

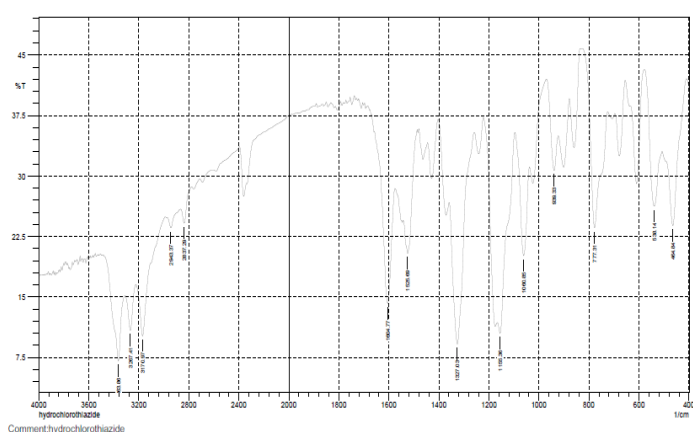
In-vitro release of Metoprolol Succinate

In-vitro dissolution studies of metoprolol succinate were performed as per the methods and time intervals mentioned in in house specifications [11-13]. Seven formulations of metoprolol succinate (layer1) tablets were prepared and dissolution studies were carried out and shown in Table 2 and Figure 3.

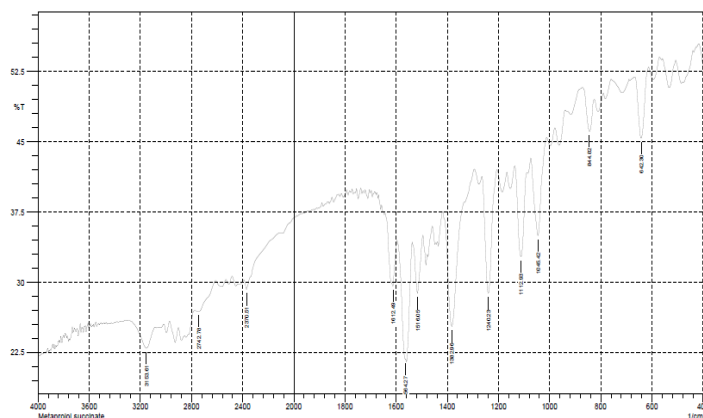
From the results it was found that the formulation trial batch F1 we found that the granules were not obtained because of the absence of binder solution so this batch was not suitable for punching. F2 showed that the release profile of the drug does not matches with the IHS limits. From the results it was showed that the drug release was in First hour $44.83 \pm 1.15\%$, for fourth hour $55.38 \pm 0.17\%$, for eight hour $82.04 \pm 1.54\%$, twelfth hour $111.09 \pm 0.04\%$. F3 formulation HPMC K-4 polymer was added in the formulations. From the results it was showed that the drug release was in first hour $39.85 \pm 0.69\%$, for fourth hour $53.68 \pm 0.64\%$, for eight hour $77.09 \pm 1.99\%$, for twentieth hour $105.95 \pm 0.01\%$. It was not found to be within the limits as per the IHS limits.

F4 formulations HPMC–K100 and HPMC K-4 concentrations were increased. The release profile of the drug does not match with the IHS limits. From the results it was showed that the drug release was in first hour $36.61 \pm 1.53\%$, for fourth hour $48.72 \pm 1.23\%$, for eight hour $70.46 \pm 1.76\%$, for twentieth hour $94.20 \pm 0.14\%$.

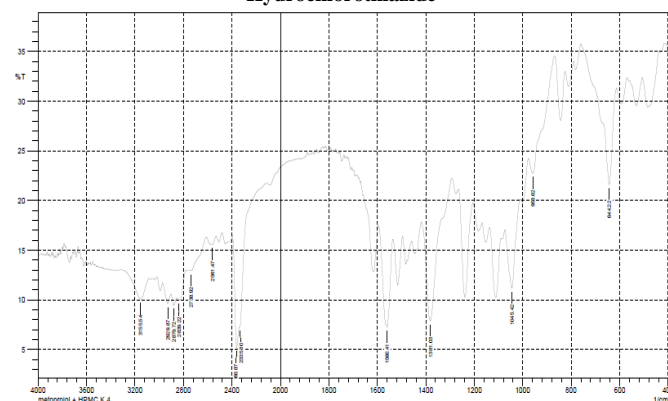
F5 formulations HPMC –K100 and HPMC K-4 concentrations were increased. The result showed four eth and eight eth hours release was not found to be match with the IHS limits. From the results it was showed that the drug release was in first hour $23.36 \pm 1.32\%$, for fourth hour $46.57 \pm 0.15\%$, for eight hour $69.67 \pm 1.26\%$, for twentieth hour $90.42 \pm 0.16\%$.



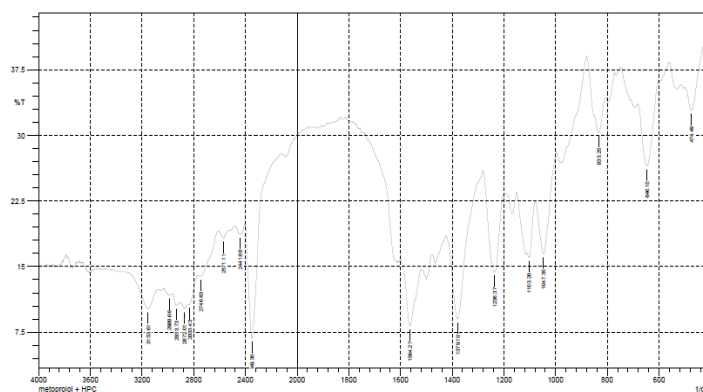
Comment:hydrochlorothiazide

Hydrochlorothiazide

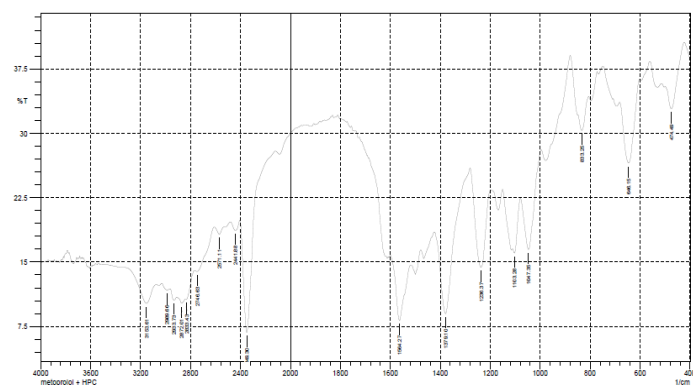
Comment:metoprolol succinate

Metoprolol Succinate

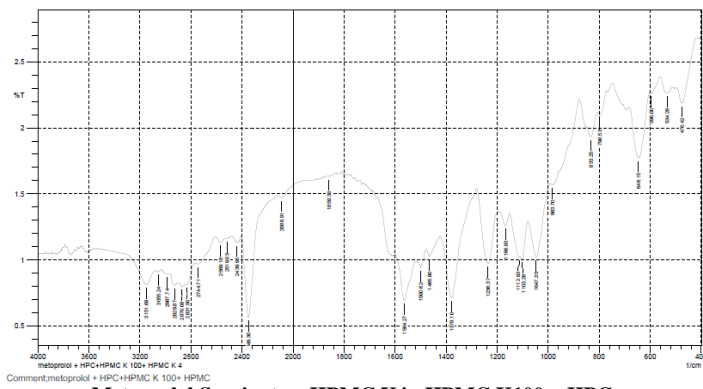
Comment:metoprolol + HPMC K 4

Metoprolol Succinate + HPMC K4

Comment:metoprolol + HPC

Metoprolol Succinate + HPMC K100

Comment:metoprolol + HPC

Metoprolol Succinate + HPC

Comment:metoprolol + HPC+HPMC K 100+ HPMC

Metoprolol Succinate + HPMC K4 + HPMC K100 + HPC

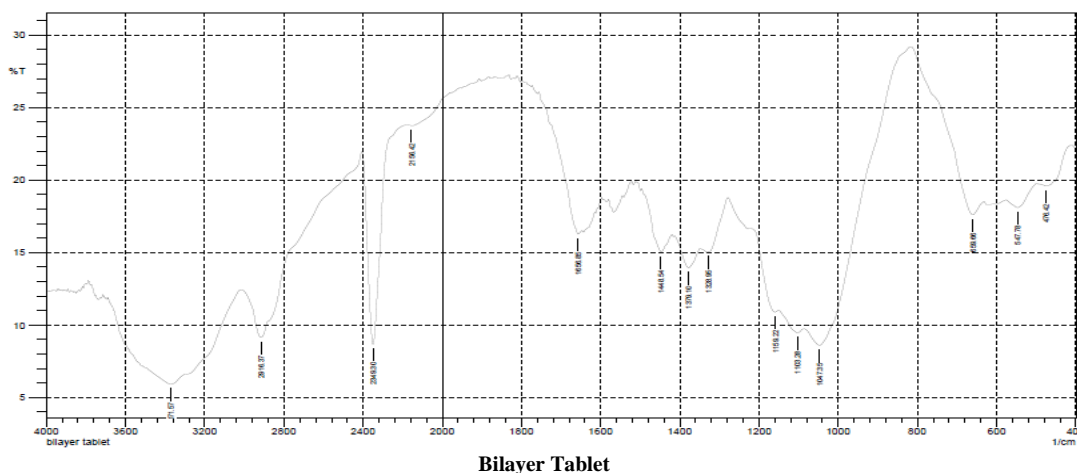


Figure 2. The FTIR Spectrum of Hydrochlorothiazide, Metoprolol Succinate with excipients and Bilayer Tablet

F6 formulations HPC polymer was used in the formulations. From the results showed the drug release was in first hour $20.44 \pm 0.05\%$, for fourth hour $44.94 \pm 0.13\%$, for eighth hour $66.91 \pm 1.20\%$, for twentieth hour $90.96 \pm 0.87\%$. The results showed eighth hour release was not found to be match with the IHS limits.

F7 formulations HPC polymer concentration was increased. From the results it was showed that the drug release was in first hour $19.79 \pm 1.08\%$, for fourth hour $40.94 \pm 1.11\%$, for eighth hour $55.82 \pm 1.45\%$, for twentieth hour $93.40 \pm 0.16\%$. The results showed that the drug release profile of all the hours release was found to be matched with the IHS limits.

In all the formulations, it was observed that the drug release rate was inversely proportional to the concentration of retarding polymer i.e., increase in concentration of retardant polymer resulted in a reduction in the drug release rate. By comparing the parameters of all the seventh formulations, F7 was showed good release characteristics as per IHS limits than all other formulations. So a formulation F7 has been selected.

Table 2 In Vitro – Dissolution Study of Metoprolol Succinate (Layer 1)

S.No.	Time of drug release	F1	F2	F3	F4	F5	F6	F7
1	I-hour	-	44.83 ± 1.15	39.85 ± 0.69	36.61 ± 1.53	23.36 ± 1.32	20.44 ± 0.05	19.79 ± 1.08
2	IV-hour	-	55.38 ± 0.17	53.68 ± 0.64	48.72 ± 1.23	46.57 ± 0.15	44.94 ± 0.13	40.94 ± 1.11
3	VIII-hour	-	82.04 ± 1.54	77.09 ± 1.99	70.46 ± 1.76	69.67 ± 1.26	66.91 ± 1.20	55.82 ± 1.45
4	XX-hour	-	111.09 ± 0.04	105.95 ± 0.01	94.20 ± 0.14	90.42 ± 0.16	90.96 ± 0.87	93.40 ± 0.16

All values are expressed as mean \pm SD (n=3)

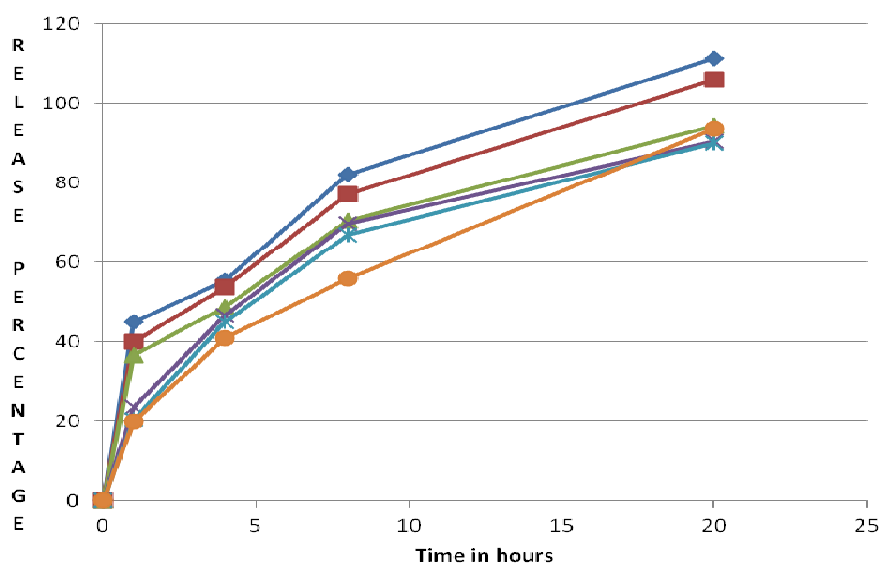


Figure 3. In-Vitro release of Metoprolol Succinate

In-vitro release of Hydrochlorothiazide

Six formulations of Hydrochlorothiazide (layer 2) tablets were prepared and dissolution studies were carried out and shown in figure 4. For the formulation trial batch F1 the drug release range was $70.96 \pm 0.02\%$ and also sticking was observed from the tablets surface. It was not found to be matching the acceptable limit[13].

F2 formulations colloidal silicon dioxide was used to the formulations. Maize starch concentration was increased. From the results it was showed that the drug release was in $72.56 \pm 0.06\%$ and slightly sticking was observed. The drug release was not observed in the complies limit. F3 formulations colloidal silicon dioxide and maize starch concentration was increased. From the results it was showed that the drug release was in $78.65 \pm 0.26\%$ and slightly sticking was observed. The drug release was not found to be the complies with in the limit.

Table 3 In-Vitro Dissolution Studies of Hydrochlorothiazide (Layer 2)

S.No.	TIME	F1	F2	F3	F4	F5	F6
1	15 min	11.87 \pm 0.04	13.98 \pm 0.12	16.98 \pm 0.26	17.12 \pm 0.68	20.87 \pm 0.65	23.41 \pm 0.12
2	30 min	26.42 \pm 0.25	32.14 \pm 0.14	37.43 \pm 0.13	41.38 \pm 0.12	49.52 \pm 0.16	48.37 \pm 0.17
3	45 min	33.67 \pm 0.31	47.35 \pm 0.61	52.21 \pm 0.23	58.91 \pm 0.15	67.32 \pm 0.42	65.20 \pm 0.46
4	60 min	70.96 \pm 0.02	72.56 \pm 0.06	78.65 \pm 0.26	80.79 \pm 0.17	93.54 \pm 0.15	96.82 \pm 0.16

All values are expressed as mean \pm SD (n=3)

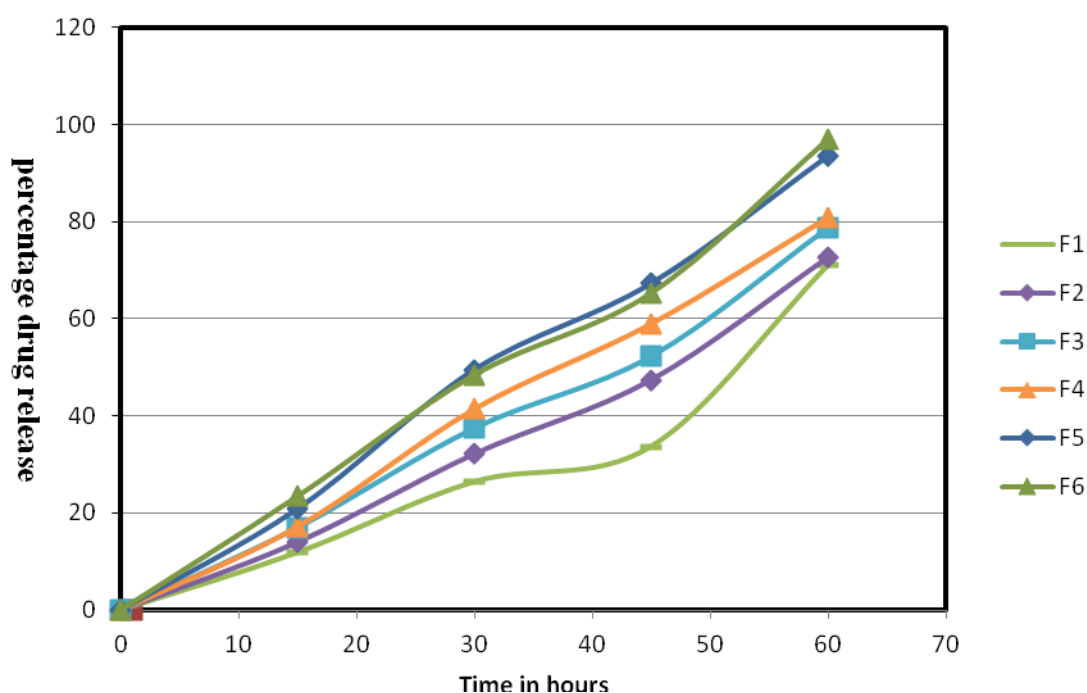


Figure 4. In-Vitro drug release of Hydrochlorothiazide IR

F4 formulations colloidal silicon dioxide concentration was increased. From the results it was showed that the drug release was in $80.79 \pm 0.17\%$ and sticking problem was overcome. The drug release was not found to be the complies with in the limit. Changes of Maize starch concentration were not found the major changes in the dissolutions. F5 formulations the method was changed. Hydrochlorothiazide was soluble in acetone and insoluble in water. So acetone was used instead of water. From the results it was showed that the drug release was in $93.54 \pm 0.15\%$.

F6 formulations maize starch and lactose concentration was increased. From the results it was showed that the drug release was in $96.82 \pm 0.16\%$. From the results F6 formulations found that the drug release was within the complies limit.

CONCLUSION

The present study was carried out to develop a bilayer tablet of Metoprolol succinate using hydrophilic matrix formers such as HPMC K100, HPC, and HPMC K 4 for the sustained release layer. Hydrochlorothiazide was immediate release formulation using starch, lactose, as a disintegrating agent. In the present investigation, bilayer tablets of metoprolol succinate sustained release and hydrochlorothiazide immediate release can be developed to

enhance drug release time and thereby improve its bioavailability. More over the frequency of administration can be reduced. The dissolution profile values of metoprolol succinate sustained release and hydrochlorothiazide immediate release bilayer tablet was within specified limits. From the FTIR studies this indicated that there was no chemical interaction or decomposition of Metoprolol succinate and Hydrochlorothiazide in the presence of polymers. From the in-vitro release studies F7 formulation of Metoprolol succinate sustained release and F6 formulation of hydrochlorothiazide immediate release optimized manufacturing processes showed good result in formulation of stable tablet dosage form.

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