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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 a 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 an immediate rise in the blood concentration. But the drug concentration in the blood is maintained at the steady-state level as the drug is released from the sustained release layer. The dose is varied upon the patient's severity conditions. It varied from metoprolol succinate 25 mg to 200 mg and hydrochlorothiazide 12.5 mg to 25 mg. A bilayer dosage form is containing Metoprolol succinate SR and Hydrochlorothiazide IR, respectively for the management of hypertension.

INTRODUCTION: The treatment of an acute disease or 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 the drug to the needed area [2].

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To achieve the goal, the dosage 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 a 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 preferred 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 some 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 an extended period [4].

MATERIALS AND METHODS:

Formulation of Metoprolol Succinate Granules:

Layer 1: Different formulations (F1-F7) were prepared with hydroxyl propyl methyl cellulose of different grads like HPMC-K_4M, HPMC-K_{100}, 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 a rapid mixer granulator for 15 minutes at a 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 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–K_4M, HPMC- $K_{100,}$ HPC, and purified talc were mixed with dried granules at 15 min. The 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 was sifted through 100 mesh. The sifted blend was allowed to mix thoroughly in a rapid mixer granulator for 15 min 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 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 min, and the 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 **Fig. 1** and **2**. Initially, the die cavity was adjusted for proper die cavity filling, and pressure adjustment was made to get the proper hardness of the tablet. Now granules are ready for compression of a bilayer tablet. Metoprolol succinate granules (layer 1) 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]. The second layer was differentiated by colored granulation. The evaluated granules were compressed using cadmech 27 stations automatic compressing machine with a 13/ 32 inch, standard circular shape with plain surface punch's and dies with compressing force 4.5 don.

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, color, presence or absence of odor, taste, physical flows and consistency [6, 7].

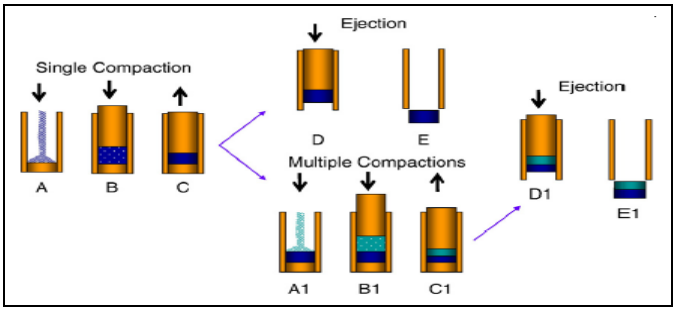


FIG. 1: BILAYER TABLET PREPARATION USING PUNCHING MACHINE

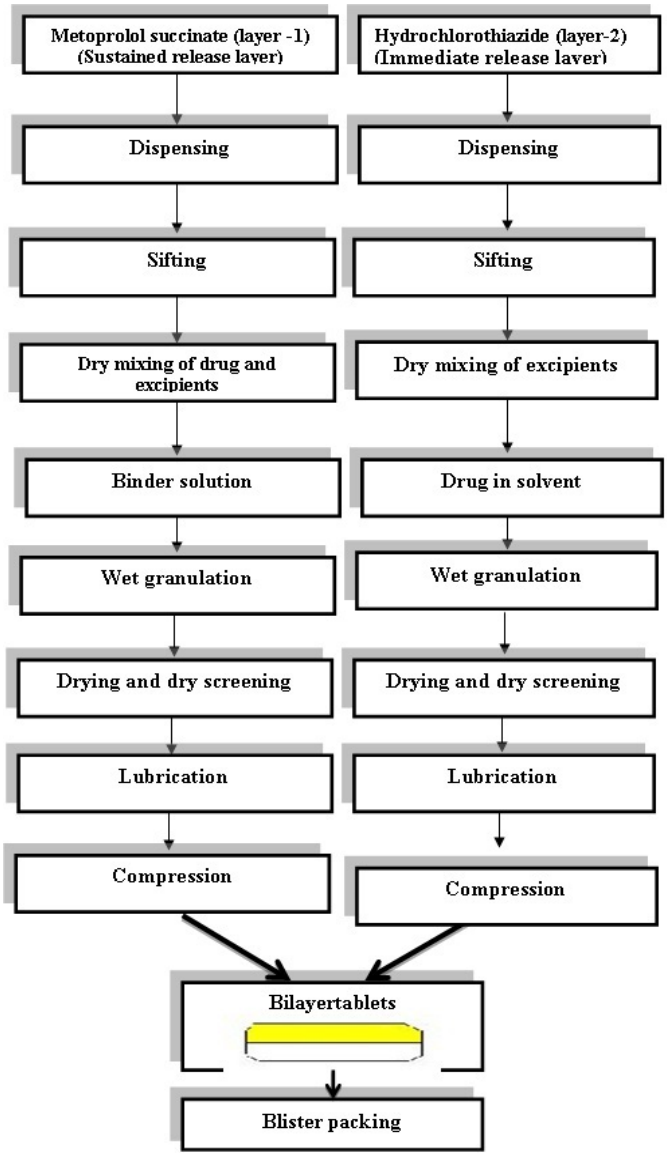


FIG. 2: BILAYER PROCESS FLOW CHART

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 break, and this force was reported.

Friability Test: Friability is the loss of weight of a tablet in the container/ package due to the 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 (w1) and placed in the apparatus where they are exposed to rolling. After 100 revolutions, the tablets are weighed (w2), and this was compared with the initial weight of the tablet. The value is expressed in percentage. A maximum loss is of weight not greater than 1% acceptable for most 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 the test; W_2 = Weight of ten tablets after the test.

Weight Variation Test: Twenty tablets of each formulation were selected at random and weighed individually. The weight of the individual tablet was noted and given in **Table 1**. 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

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

TABLE 1: 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

The 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 the preparation of sample and spectra were recorded over the wave number 4000 to 500 cm^{-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 the mixture when compared to the pure drug, it indicates the absence of interactions [9].

Metoprolol Succinate and Hydrochlorothiazide Bilayer Tablet Evaluation: 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 2**.

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 a blue color. 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 was the results found that range between 374.70 ± 3.25 to 377.00 ± 1.15 mg. It was proved that the IP limit and compiles the test. The accepted percentage deviation of the tablet was ± 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 was 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 compiles the test.

Hardness: From the results of hardness, it was found that the formulated trial batch F2 to F7 was the results found that range between 4.85 ± 0.25 to 5.36 ± 0.22 kg/cm^2. It was proved that the in-house specifications and compiles the test.

Friability Test: From the results of friability, it was found that the formulated trial batch F2 to F7 was 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 compiles the test.

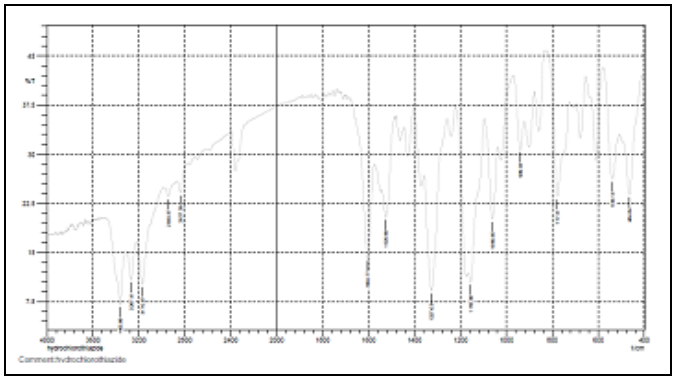
Drug Content: From the results obtained from the formulations F2 to F7 the maximum and minimum range was in metoprolol succinate 98.91 ± 1.67 to 103.32 ± 1.24% and hydrochlorothiazide was 92.47 ± 0.32 to 107.15 ± 1.36% using HPLC method. The drug content of metoprolol succinate equivalent to metoprolol tartrate and hydrochlorothiazide tablet range between 90.0% to 110.0% limit described in the USP. It was matched in USP mentioned a 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.

IR 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 the formulation of a 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 shown in **Fig. 3**.

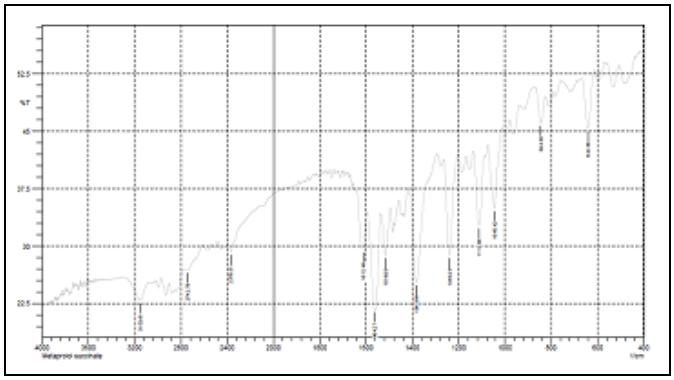
TABLE 2: EVALUATIONS OF BILAYER TABLETS OF METOPROLOL SUCCINATE SR AND HYDROCHLOROTHIAZIDE IR

S. no.	Parameters	Specification	F1	F2	F3	F4	F5	F6	F7
1	Description	Blue / white colored 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
2	Weight variation (mg)	375 mg ± 5%	-	375.2 ±2.50	376 ±1.73	374.70 ±3.25	377.00 ±1.15	376.5 ±4.06	375.20 ±2.23
3	Thickness (mm)	4.8mm ± 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
4	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
5	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
6	Drug content		-						
	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
	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

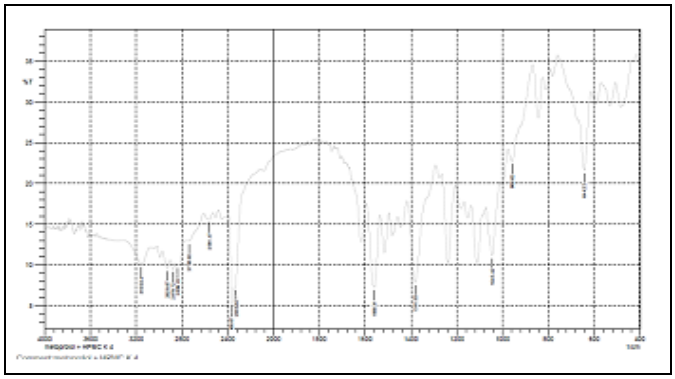
All the values are mean ± SD (n=3)



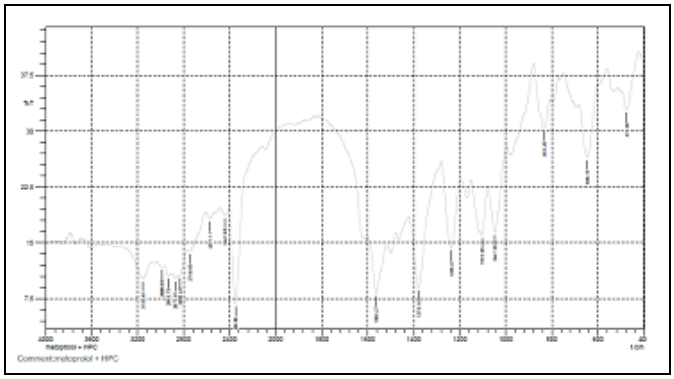
HYDROCHLOROTHIAZIDE



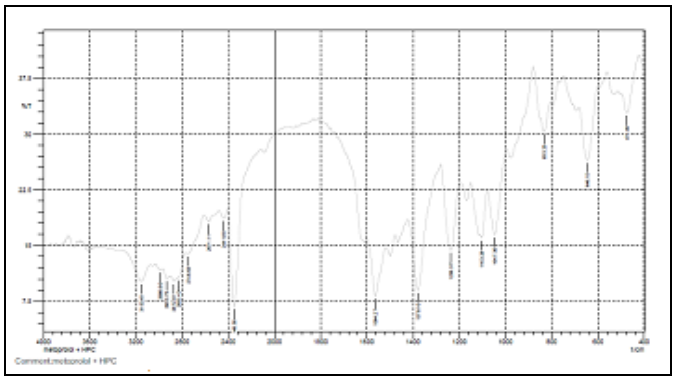
METOPROLOL SUCCINATE



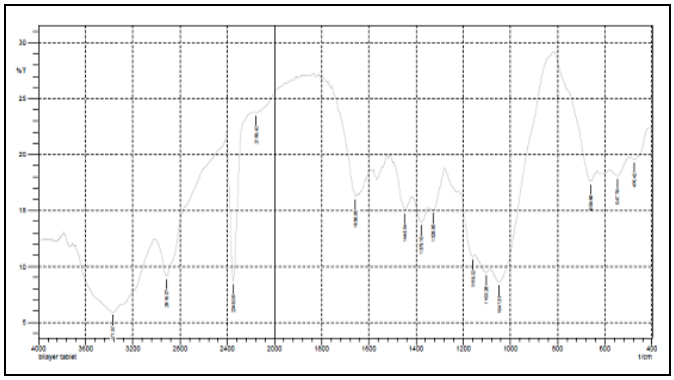
METOPROLOL SUCCINATE + HPMC K4



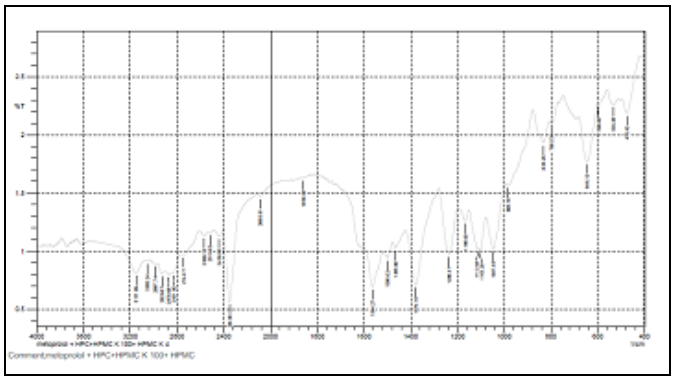
METOPROLOL SUCCINATE + HPMC K100



METOPROLOL SUCCINATE + HPC



BILAYER TABLET



METOPROLOL SUCCINATE + HPMC K4 +HPMC K100 + HPC

FIG. 3: THE FTIR SPECTRUM OF HYDROCHLOROTHIAZIDE, METOPROLOL SUCCINATE WITH EXIPIENTS AND BILAYER TABLET

***In-vitro* Release Studies:** *In-vitro* release studies were performed to evaluate the dissolution character of metoprolol succinate and Hydrochlorothiazide from bilayer tablets and comparing marketed sample. The result of the *in-vitro* release studies of all Formulations is presented in **Table 3** and **4**.

***In-vitro* Release of Metoprolol Succinate:** *In-vitro* dissolution studies of metoprolol succinate were performed as per the methods and time intervals mentioned in-house specifications [11, 12, 13]. Seven formulations of metoprolol succinate (layer1) tablets were prepared, and dissolution studies were carried out and shown in **Fig. 4**.

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 match with the IHS limits. From the results it was shown that the drug release was in First hr 44.83 ± 1.15%, for fourth hour 55.38 ± 0.17%, for eight hours 82.04 ± 1.54%, twelfth hour 111.09 ± 0.04%. F3 formulation HPMC K-4 polymer was added in the formulations. From the results, it was shown that the drug release was in first hour 39.85 ± 0.69%, for fourth hour 53.68 ± 0.64%, for eight hours 77.09 ± 1.99%, for twentieth hour 105.95 ± 0.01%. It was not found to be within 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 shown that the drug release was in first hour 36.61 ± 1.53%, for fourth hour 48.72 ± 1.23%, for eight hours 70.46 ± 1.76%, for twentieth hour 94.20 ± 0.14%. F5 formulations HPMC-K100 and HPMC K-4 concentrations were increased. The result showed fourth and eight eth hours release was not found to be matched with the IHS limits. From the results, it was shown that the drug release was in first hour 23.36 ± 1.32%, for fourth hour 46.57 ± 0.15%, for eight hours 69.67 ± 1.26%, for twentieth hour 90.42 ± 0.16%.

F6 formulations HPC polymer was used in the formulations. From the results showed the drug release was in first hour 20.44 ± 0.05%, for fourth hour 44.94 ± 0.13%, for eight hours 66.91 ± 1.20%, for twentieth hour 90.96 ± 0.87%. The results showed eight-hour release was not found to be matched with the IHS limits.

F7 formulations HPC polymer concentration was increased. From the results, it was shown that the drug release was in first hour 19.79 ± 1.08%, for fourth hour 40.94 ± 1.11%, for eight hours 55.82 ± 1.45%, for twentieth hour 93.40 ± 0.16%. The results showed that the drug release profile of all the hour's 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 the 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.

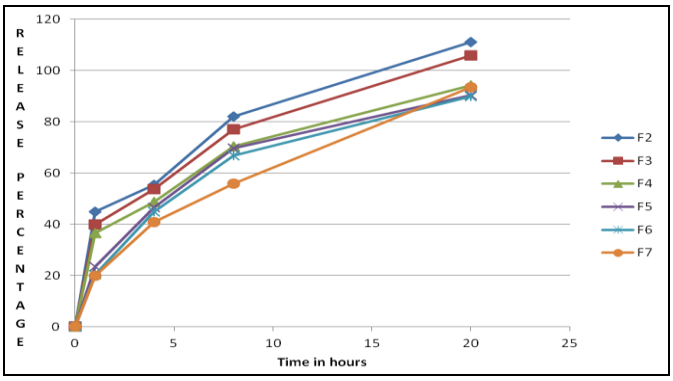


FIG. 4: *IN-VITRO* RELEASE OF METOPROLOL SUCCINATE

TABLE 3: *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 ±SD (n=3)

***In-vitro* Release of Hydrochlorothiazide:** Six formulations of Hydrochlorothiazide (layer 2) tablets were prepared, and dissolution studies were carried out and shown in **Fig. 5**. For the formulation trial batch, F1 the drug release range was 70.96 ± 0.02% and also sticking was observed from the surface of the tablet. 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 shown that the drug release was in 72.56 ± 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 shown that the drug release was in 78.65 ±0.26% and slightly sticking was observed. The drug release was not found to be the complies within the limit.

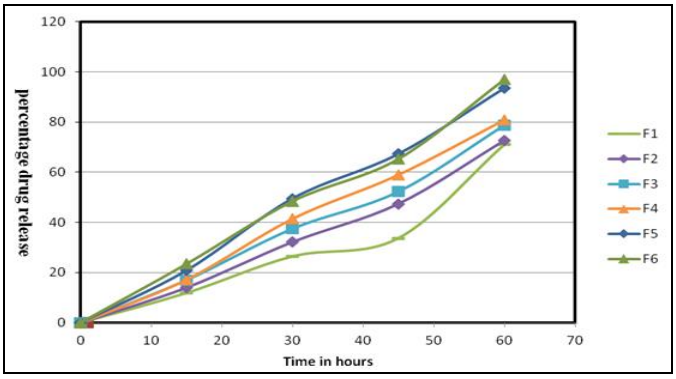


FIG. 5: *IN-VITRO* DRUG RELEASE OF HYDRO-CHLOROTHIAZIDE IR

TABLE 4: *IN-VITRO* DISSOLUTION STUDIES OF HYDROCHLOROTHIAZIDE (LAYER 2)

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

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

F4 formulations colloidal silicon dioxide concentration was increased. From the results, it was shown that the drug release was in 80.79 ± 0.17% and the sticking problem was overcome. The drug release was not found to be the complies within 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 shown that the drug release was in 93.54 ± 0.15%. F6 formulations maize starch and lactose concentration was increased. From the results, it was shown that the drug release was in 96.82 ± 0.16%. From the results, F6 formulations found that the drug release was within the complies limit.

CONCLUSION: The study was developed by selecting the HPMC K4 and HPMC k100 and HPC as a polymer. Based on the properties of the drug and polymer wet granulation method was selected for the study. The granules were prepared, and the preformulation studies were carried out. Preformulation studies such as the angle of repose, bulk density, tapped density, compressibility index, and the hausner ratio were performed as per the standard procedure, and the results showed that all the parameters are within the specified limits.

- Tablets were evaluated for hardness test, friability test, and thickness test, uniformity of weight, drug content estimation, and dissolution study. All the parameters complied with the test.

- When comparing all among the formulations, F7 formulations of Metoprolol succinate sustained release, and F6 formulation of hydrochlorothiazide immediate release the precompression parameters of the bulk density, angle of repose, tapped density, compressibility index, and Hausner ratio were the results showed within limits. The results of post-compression parameters such as hardness test, friability test, thickness test, uniformity of weight were within limits. By comparing the drug content of the all among the formulations F7 Metoprolol succinate were 103.32 ± 1.24%, and F6 hydrochlorothiazide was 107.15 ± 1.36% using HPLC method, the results were shown within the USP limit. By comparing the in-vitro drug release of all among the formulations F7 Metoprolol succinate was showed good release characteristics as 20^{th}-hour release was 93.40 ± 0.16%, and F6 hydrochlorothiazide showed excellent release characteristics as 60 min 96.82 ± 0.16% using USP paddle II apparatus by HPLC method. The results were shown within the in house

specification limit. So, from the above results, formulation F7 Metoprolol succinate and F6 hydrochlorothiazide have been selected.

- All the formulations were subjected for stability studies up to three months at different temperatures such as accelerated stability (40°C/75% RH) and real-time stability(30°C/65% RH). On Initial, 1 month, 2 month, 3 months the drug content and dissolution studies were carried out. There was no significant change in the drug content and *in-vitro* drug release after 3 months. It showed that all formulations are stable.

ACKNOWLEDGEMENT: None

CONFLICT OF INTEREST: None

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