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Formulation and Evaluation of Controlled Release Matrix Tablets Containing Sotalol Hydrochloride

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Abstract: ***The present research work, formulation and Evaluation of controlled release matrix tablets containing Sotalol hydrochloride for the treatment of Arrhythmiasis. Sotalol has both property of blocking beta-adrenoreceptor and prolongation of cardiac action potential and antiarrhythmic properties. The controlled release matrix tablets of sotalol hydrochloride were prepared using wet granulation technique. Physico chemical characterization of tablet and powder blends used to form the matrix tablet was carried out using a range of experimental techniques. The prepared granules were evaluated for Bulk density, Tapped density, Compressibility index, and Hausner's ratio. The controlled release tablets were tested for weight variation, thickness, hardness and friability as per official procedure. The Instacoat EN II polymer was used as enteric coat polymer for coating the matrix tablet. The coated tablets were subjected for in-vitro drug releases studies. Dissolution studies of sotalol hydrochloride controlled release tablets in media with different dissolution media 0.1 N HCl, pH (7.4) as per US Pharmacopeia. The study showed that, drug releasein 2hr was highly affected by the coating level. The dissolution data reveled that the% of coating, ratio of polymers and concentration of Compritol 888 ATO are very important to achieve optimum formulation. The matrix tablets of Sotalol hydrochloride were prepared using wet granulation. . Tablets were tested for weight variation, thickness, hardness and friability as per official procedure. Instacoat EN II was used as enteric coat polymer for coating the matrix tablet. The coated tablets were evaluated for in-vitro drug release profile. Dissolution studies of controlled release Sotalol hydrochloride matrix tablets were carried out in different dissolution media 0.1 N HCl and pH 7.4 as per US Pharmacopiea. The results showed that, drug release in 2 hrs was highly affected by the coating level. The dissolution data revealed that the% of coating, ratio of polymers and concentration of Compritol 888 ATO are key factors to achieve optimum formulation.***

Keywords: Sotalol hydrochloride, controlled release, Arrhythmiasis, matrix tablet

1. Introduction

The formulation of controlled-release delivery systems is dependent on several variables of significant importance. They include route of drug delivery, the type of formulation, the disease to be treated, condition of the patient, duration of therapy and the characteristics of the drug. Each of these variables are complementary to each other and this exploits certain restrictions upon selection for the route of delivery, the design of the formulation and the duration of therapy. Characteristics of the drugs play a significant role in designing a controlled release dosage form mainly physicochemical and biological properties of the drug are of primary importance.

Sotalol has both property of blocking beta-adrenoreceptor and prolongation of cardiac action potential and antiarrhythmic properties. The controlled release matrix tablets of sotalol hydrochloride were prepared using wet granulation technique. Sotalol blocks response to adrenergic stimuli by combatively blocking β1-adrenergic receptors inside the myocardium and β2-adrenergic receptors within bronchial and vascular smooth muscle. The electrophysiologic response of sotalol may be due to its judicious inhibition of the immediately activating component of the potassium channel convoluted in the repolarization of cardiac cells. The class II electrophysiologic responses are acquired by an escalation in sinus cycle length (slowed heart rate), decreased AV nodal conduction, and escalated AV nodal refractoriness, while the class III electrophysiological effects involves amplification of the atrial and ventricular monophasic action potentials, and effective refractory period amplification of atrial muscle, ventricular muscle, and atrio-ventricular accessory pathways in both the anterogradeand retrograde directions. Here an attempt was made to lower the dosing frequency and to control the drug level at therapeutic concentration range, by formulating and designing a Controlled drug delivery system in the form of matrix tablets.

2. Methodology

Determination of λ (lambda max) of Sotalol Hydrochloridein pH 7.4 buffer

The stock solution of Sotalol was prepared by dissolving 10 mg Sotalol in 100ml with respective buffer. From this stock solution of Sotalol serial dilution were prepared to obtain a dilution range of 2-10µg/ml employing respective buffer solutions. All samples were interpreted by UV spectrophotometer by checking the absorbance at 247 nm.

Preparation of matrix tablets.

Sifting; Sift of all the ingredients

Checking of Weights; Check the weights

SieveNo.
Sotalol hydrochloride 24#
Lactosemonohydrate 30#
HPMC K4 M 30 #
HPMC K100 M 30 #

Dry Mixing: Mix the material into the blender at slow speed for 10 minutes

Granulation: The binder solution was prepared and supplemented to the above dried mixed ingredients and makes them as wet mass. The wet mass was screened through Sieve No: # 8 and kept to dry for 1 hour. Then it was rasped using sieve No: # 20

Mixing of extragranular material: The prepared granules were mixed with extra granular material for 5 min.

Lubrication: After mixing of extra granular material the blend was lubricated by using magnesium stearate for 5 min.

Compression: Proceed to commence Compression operation on Rotary Tablet compression machine using Capsular shape of Standard Concave punch sets bearing break line on single side.

Table 1

Ingredients	F1 (mg/tab)	F2 (mg/tab)	F3 (mg/tab)	F4 (mg/tab)	F5 (mg/tab)	F6 (mg/tab)
Sotalol HCl	25	25	25	25	25	25
Hydroxy propyl methyl celluloseK4M	16.5	16.5	22	22	22	22
Glyceryl Behenate	10	10	14	12	12	10
LactoseMonohydrate	121.5	119.5	110	112	114	114
Poly vinyl pyrolidine	4	4	4	4	4	4
Magnesium Stearate	2	2	2	2	2	2
Aerosil 200	2.5	2.5	2.5	2.5	2.5	2.5
Talc	3.5	3.5	3.5	3.5	3.5	3.5
Sodium starch Glycolate	6	6	6	6	6	6
Total weight (mg)	200	200	200	200	200	200

Differential Scanning Calorimetry (DSC)

DSC is a method in which the contrast in heat flow between the sample and a reference is recorded versus temperature. All dynamic DSC studies were performed on Du Pont thermal analyzer with 2010 DSC module. Calorimetric measurements were carried out with empty cell as the reference. The equipment was calibrated utilizing high purity indium metal as standard. The dynamic studies were carried out in nitrogen atmosphere at the heating rate of 10º C/Min. The trials were done in triplicate. The temperature of scanning for reference pure drug and formulation are identical when dynamic measurements are performed, and therefore the required heat energy for chemical transformation is reported on a heat flow versus temperature graph. The energy is reported as Joules per kilocalorie.

Uniformity of thickness:

Diameter and thickness of both coated tablets and core tablets were recorded using a calibrated vernier caliper. Three tablets of each formulation were picked in a randomized manner and dimensions were determined. It is denoted as mm and standard deviation was also calculated.

Weight variation test:

Weight variation was carried by using 20 tablets of each formulation batch. the tablets were weighed individually using a digital weighing balance.

Hardness test:

Hardness denotes the capability of a tablet to withstand mechanical shocks while handling and transporting. Hardness of core tablets was determined using a validated hardness tester. It is expressed in Nkg/cm2. Three tablets were picked randomly from each batch and subjected for hardness. The mean and standard deviation were also calculated for each batch.

Friability test:

For each tablet formulation batch, the friability of 6 tablets was determined.

Friability of the tablet can be determined by following equation:

$$F = \frac{W(I) - W(F)}{W(I)} \times 100$$

Trials of Coating:

Tablet coating was carried out using Instacoat EN II. Three different formulations were formulated by varying the weight gain on tablet upon coating. The coated tablets were subjected for *in-vitro* drug release profile.

Table 2: Coating Solution Composition

Insta coat EN II W/W	10%
IPA W/W	90%

Weighed quantity of readymade enteric coating material is slowly and constantly mixed with 90% w/w of IPA by using a mechanical stirrer. Coating solution prepared is allowed stand for two and half hour and then the coating solution is passed through mesh No: 100 # to eliminate solid material.

Coating Parameter:

Clean & operate the coating pan. Switch on the blower so as to start hot air supply (30-35°C) on tablet bed for about 10 minutes. Tablet bed should be headed to 25-30°C.

Process of coating:

Start compressed air & exhaust.

Start the Spray of the solution and maintain the following parameters,

- Pan speed 25-30 rpm
- Tablet bed temperature 25 – 30°C
- Distance of gun from bed About 12 – 15 cm.
- Atomizing pressure 1.5 Kg/cm2

- Exhaust On
- Inlet air temperature 30-35° C
- Direction of spray pattern 90° to tablet bed

Observe the spray gun for chocking, if any chocking observed during the coating process, immediately stop the coating process. After completion of spraying the total volume of solution cease the compressed air. The tablets are subjected for Rolling for another 5-10 minutes for complete drying. After achieving the desired weight gain note the average weight of coated tablet.

***In-vitro* drug release studies of tablets:**

In-vitro Drug release of coated tablets were carried out using a USP XXIII dissolution rat test apparatus (Apparatus 2, 100 rpm, 37 +1°C) for 2 hrs in 0.1 N HCl acidic buffer (900 ml) as the average gastric emptying time is about 2 hrs. Then the dissolution medium was changed with pH-7.4 basic buffer (900 ml) which mimic the intestinal environment for 7 hrs tested for drug release up to complete drug release. At specific time interval of I hr, 10 ml of the samples were taken and analyzed for Sotalol hydrochloride content. A 10 ml fresh and filtered dissolution medium was added to make the Volume after each sample withdrawal which marginally mimics the sink conditions. The collected Samples were analyzed using UV spectrophotometer at 247 nm.

3. Results and Discussion

Ultraviolet spectroscopy

Accurately weighed 10 mg of Sotalol Hydrochloride was transferred to a 100 ml volumetric flask and 1% of tween80 was added to enhance the solubility of Sotalol Hydrochloride (stock solution), from the stock solution 3ml of the sample was taken and added to the 50ml volumetric flask and volume made up to the mark with phosphate buffer. The scanning was done from 200-400 nm. The sharp peak was observed at 247.0 nm, which was considered as λ max.

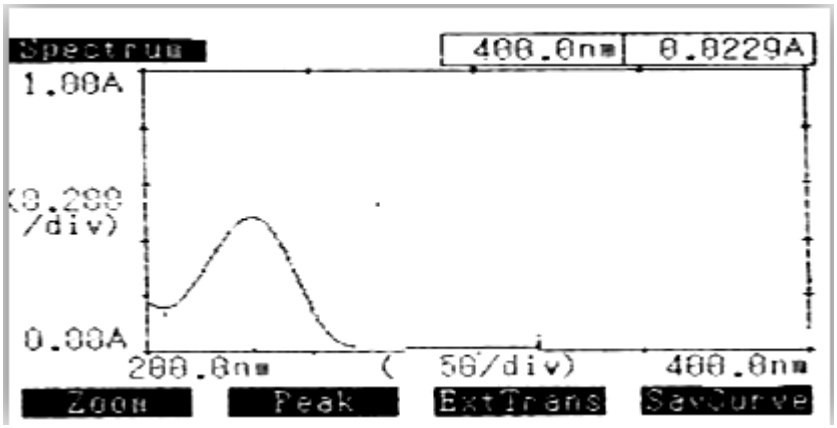

Figure 1: UV absorption spectra of Sotalol Hydrochloride

Drug-excipient Compatibility Studies

The compatibility between the drug and polymers under experimental conditions is essential pre requisite for formulation. It is therefore important to confirm that the drug does not react with the polymers and excipients under experimental conditions and affect the shelf life of product or any other unwanted effects on the formulation. The DSC thermograms of the pure drug and formulation were taken, the obtained results indicates that there were no significant interactions between drug and polymer.

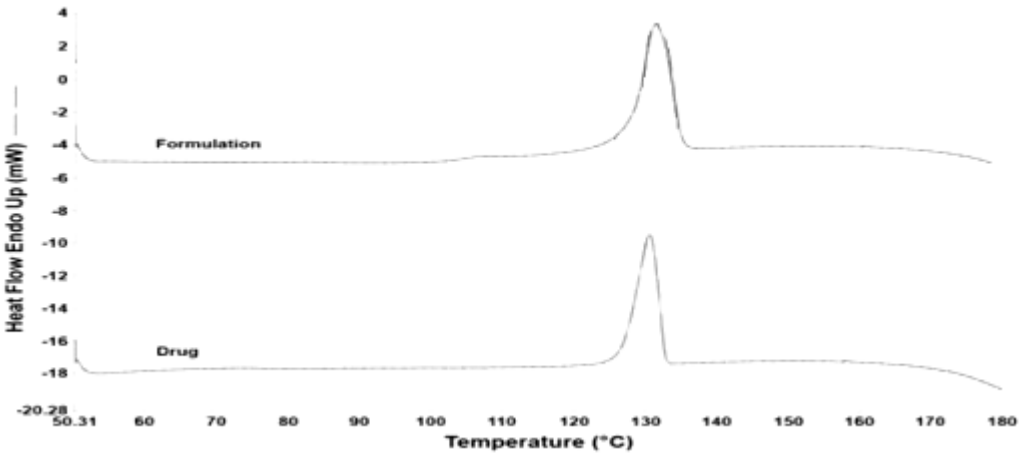

Figure 2: DSC Thermograms of pure drug and the formulation

Evaluation of the Prepared Tablets

Post-compressional parameters:
All the tablet formulations were subjected for evaluation according to various official specifications and other parameters. Shape, thickness, hardness, friability, weight variation, tablet dosage form assay.

Disintegration time: Disintegration time of coated tablets was found to be3hr 49 min.

Shape and appearance: Formulations prepared were randomly picked from each batch examined under lens for shape and in presence of light for color. Tablets showed capsule shape. Tablets were white in color.

Uniformity of thickness: Thickness of the tablets was measured using calibrated thickness gauge by picking three tablets randomly from all the batches. The results of thickness for tablets are shown in Table. The mean thicknesses of tablets were lies between 4.09±0.04 mm to 4.12±0.07 mm. The standard deviation values indicated that all the formulations were within the range.

Weight variation test: The weight variation of uncoated tablets all the formulations is shown in Table. The result lies between 198±2 mg to 204±2 mg. All the tablets passed the weight variation test, i. e., average percentage weight variation was found within the pharmacopoeial limits of ±7.4%.

Hardness test: Hardness or crushing strength of the tablets of both the formulation was found to belies between 150±5 N kg/cm^2 to 156±4 N kg/cm^2. The mean hardness test results are tabulated in Table.

The low standard deviation values indicated that the hardness of all the formulations was almost uniform and the tablets possess good mechanical strength with sufficient hardness.

Friability test: Friability values for batch were found to belies between 0.066% to 0.078 % respectively. The obtained results were found to be well within the approved range (<1%) in all the designed formulations. That indicated tablets possess good mechanical strength. The results are tabulated in Table.

Table 3: Quality Control Test for Tablets

Formulation	Thickness (mm)	Weight of tablet (mg)	Friability (%)	Hardness (N Kg/cm^2)	Assay (%)
F1	4.14±0.07	200 ± 2	0.066 ±0.005	152 ± 4	100.20%
F2	4.09 ±0.04	198± 2.51	0.074 ±0.001	153 ± 2	99.50%
F3	4.12±0.04	202 ± 1	0.0659±0.0063	150 ± 5	99.30%
F4	4.11 ±0.04	200.3 ±1.52	0.077±0.014	156 ± 4	99.50%
F5	4.12±0.05	201 ± 2.64	0.078 ±0.0075	155 ± 3	99.80%
F6	4.12 ±0.07	204 ± 2	0.069 ±0.005	154 ± 4	101.20%

In-vitro drug dissolution
The i*n-vitro* release studies were carried out using – XXIII dissolution assembly, Coating of tablets with Instacoat EN II showed the release about of nearly 6.6 % in 2 hr and use of different ratio of Methocel and Compritol showed release after 9 hr was 99.66%. From the result, concluded that Coating of tablets with Instacoat EN II, use of different ratio of Methocel and Compritol can be successfully utilized to create desire release profile at 2 hr and 9 hr similar to the targeted release profile in further study. The results obtained in the *in-vitro* drug release study are tabulated in Table.

Table 4: *In-vitro* Drug Release Studies

Dissolution medium	Time (hrs)	F1	F2	F3	F4	F5	F6
0.1 N HCl	1	0	0	0	0	0	0
	2	6.06±1.40	3.52±1.23	5.78±1.06	4.21±0.97	4.84±0.73	5.12±0.52
7.4 Tris buffer	3	17.60±0.92	15.45±0.88	16.87±0.51	14.7±0.64	13.07±0.43	14.31±0.31
	4	28.34±0.32	23.93±0.68	31.33±0.49	29.15±1.76	21.53±1.54	22.23±1.84
	5	46.40±1.72	41.0±0.81	48.24±1.34	40.27±1.56	42.49±1.23	39.64±0.75
	6	61.51±1.21	59.16±1.09	63.12±1.11	59.25±0.76	58.35±1.13	57.85±1.07
	7	74.6±0.32	77.49±1.4	72.41±1.36	73.1±0.88	76.41±1.79	71.49±1.25
	8	89.30±0.88	82.21±1.79	85.34±1.62	88.44±0.67	87.63±0.72	83.42±0.54
	9	97.09±0.84	94.45±1.21	98.34±1.38	99.13±1.79	95.14±1.92	99.66±0.51

4. Conclusion

The study was undertaken with an aim of Formulation Development and Evaluation of Sotalol controlled release tablets using different polymers as release retarding agent. Tablets were tested for weight variation, thickness, hardness and friability as per official procedure. After compression tablets are subjected for enteric coating to mask the release of drug in stomach. Dissolution was carried out in pH 7.4 buffer Media. Based on dissolution tests, it was concluded that F4 satisfactorily release drug through 9 hrs.

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