FORMULATION AND EVALUATION OF QUINIDINE OSMOTIC DRUG DELIVERY SYSTEM

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ABSTRACT : Quinidine which is antiarrhythmic agentselected as a model drug to prepare controlled porosity osmotic pump (CPOP) tablet. The effect of different formulation variables - such as the level of solubility modifier in the core, membrane weight gain, and level of pore former in the membrane - were studied. Drug release was found to be affected by the level of solubility modifier present in the core. Quinidine release was inversely proportional to the membrane weight but directly related to the initial level of pore former (in the membrane). Controlled porosity osmotic pump (CPOP) based drug delivery system contains active ingredient, osmogens, semi permeable membrane, channelling agent and water soluble additives. In this system, when water comes in contact with water soluble additives it results in an in situ formation of a Microporous membrane. The main driving force for the release of drug is osmotic pressure. Osmogens maintain concentration gradient across the membrane. The present study deals with Controlled porosity osmotic pump tablets and its basic components.

Key words: Quinidine, osmotic drug delivery,osmosis, direct compression technique, coating and in vitro drug release studies.

I.INTRODUCTION

Oral controlled release systems continue to be the most popular amongst all the drug delivery systems because pharmaceutical agents can be delivered in a controlled pattern over a long period by osmotic pressure, there has been increasing interest in the development of osmotic devices over the past 2 decades. Osmotic drugdelivery systems (OSCDDS) discharge the drug with the zero order kinetics which does not depend on the initialconcentration and the physiological factors of GIT. [1] Osmotic drug delivery systems (OSCDDS) discharge the drug with the zero order kinetics which does not depend on the initialconcentration and the physiological factors of GIT. [2] One of the most promising and effective dosage form is osmotic pump controlled release preparation which is not only independent of all the physiological and physiochemical factors but also modulate the rate and pattern of drug release by optimizing the process and formulation parameters such as solubility, concentration and osmotic pressure of the core component(s), size of the delivery orifice, and nature of the rate-controlling membrane. [3]The osmotic drug delivery systems suitable for oral administration typically consist of a compressed tablet core that is coated with a semipermeable membrane that has an orifice drilled on it by means of a laser beam or mechanical drill. [4]Osmotic pump drug delivery technologies can also be used to deliver high drug doses meeting high drug loading requirements. [5] Osmotic pumps are controlled drug delivery devices based on the principle of osmosis. Wide spectrums of osmotic devices are in existence. Amongst them, the osmotic pumps are unique, dynamic and widely employed in clinical practice. [6] In the present investigation, an attempt will be made to design a simplified controlled porosity osmotic system of Quinidine and development of sustained release tablet dosage, which is expected to improve patient compliance due to reduced frequency. [7]

II. MATERIALS AND METHODS

Quinidine was collected as a gift sample from Hetero labs, Hyderabad and various excipients like sodium alginate, tragacanthand hydroxyl propyl methyl cellulose were purchased from AR chemicals, Hyderabad.

Methodology

Pre compression parameters[8,9,10]

Angle of repose: Weighed amount of the drug was transferred through a funnel kept at a height 2 cm from the

base. The material is transfer till it forms a heap and touches the tip of the funnel. The radius the base of the conical pile, and the height of pile were measured.

$$\tan\theta = h/r$$

Where

h= height of the pile
r= radius of the base of the conical pile
θ= angle of repose

Bulk density and Tapped density

Weighed amount of the Quinidine was transferred into 100 ml measuring cylinder without significant mechanical stresses during transfer. The volume employed by the drug was measured, and then control to 500, 750, 1250 taps in the tap density tester (electro lab USP), the blend was subjected to 500, 750 taps respectively. Then the % variation in volume was calculated, if it is more than 2 then the blend has to be subjected for 1250 taps and the percentage variation in volume has to be calculated.

Bulk density is denoted by (ρ_i)
(ρ_i) =m/v_i
Tapped density is denoted by c
(ρ_t) =m/v_t
m=mass of the blend
v_i= initial volume
v_t=tapped volume

Compressibility index (CI)

The compressibility index was expressed in percentage calculated using the formula

$$CI = \left(\frac{v_i - v_t}{v_i} \right) \times 100$$

$$CI = \frac{TD - BD}{TD} \times 100$$

Hausner's ratio

It is measured by the ratio of tapped density and bulk density.

$$\text{Hausner's ratio} = \left(\frac{v_i}{v_i} \right) \text{or} \frac{TD}{BD}$$

Drug - excipient compatibility studies[11]

The IR absorption spectra of the Quinidine drug and with different and excipients were taken in the range of 4000-450 cm^{-1} using KBr disc method. 1-2 mg of the substance to be examined was triturated with 300-400 mg of specified quantity of finely powered and dried potassium bromide. These quantities are usually sufficient to give a disc of 10-15mm diameter and pellet of suitable intensity by a hydraulic press. The scans were evaluated for presence of principle peaks of drug, shifting and masking of drug peaks due to presence polymers and excipients.

Formulation development

Table-1: Formulation of the Quinidine osmotic pump core tablets

Ingredients	F1	F2	F3	F4
Quinidine	50	50	50	50
HPMC	100	-	-	50
Sodium alginate	-	100	-	50
Tragacanth	-	-	100	-
Nacl	10	10	10	10
Magnesium stearate	3	3	3	3
Lactose	135	135	130	130
Talc	2	2	2	2
Total wt	300	300	300	300

Preparation of Quinidine tablets:[12,13]

Drug layer composed of Quinidine. Polymers are weighed accurately and passed through 44#. Pass Sodium chloride through 60# and mixed properly. The powder is lubricated with Magnesium stearate and talc as a glidant, which is passed through 60#. Blend it in a blender for 5 minutes. The prepared blend was placed in die cavity and compressed by 6 mm round standard concave punches.

Evaluation parameters:[14,15,16]

Weight variation: The prepared osmotic pump tablets are under kept for the weight variation study. Randomly about 20 tablets are taken and measure the individual weight of the tablet. Average weight of all the tablets were taken and %weight variation is calculated by the formula

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

Dimensions: The prepared tablets are under kept for theThickness by using Verniercallipers.

Hardness test: Thehardness test is also done by using Pfizer hardness tester. The six Tablets were randomly selected from each batch and hardness of each tablet was determined by using a Pharma instruments.

Friability test: The friability test is done by using the friability apparatus. The test is for the knowing of the strength of the tablets. The 10-15 tablets are taken and measure the individual weight of the tablets that is initial weight after that the measured tablets are poured in the Roche friability apparatus. It is operated at 25 rpm for 4mins about 100 revolutions. Tablets were de-dusted and weighed again. The following equation is used for the calculating of the % friability,

$$\mathbf{F} = \frac{\text{Initial wt} - \text{final wt}}{\text{Initial wt}} \times \mathbf{100}$$

Drug content estimation: The Quinidine tablets were tested for their drug content. Take 20 tablets and crush them properly. From crushed powder take 100 mg of the powder that equivalent to the Quinidine drug substance. The powder is taken in the 100ml of the volumetric flask with the 6.8 pH phosphate buffer solution. The phosphate buffer solution is kept on the sonication for 30mins. The 1ml of solution is taken and it is kept for the absorbance in U.V visible spectroscopy at 230 nm.

***In-vitro* Dissolution studies:**[17]*In vitro* drug release studies are performed by using USP-II apparatus paddle type. The prepared tablets are under kept in the dissolution studies. The sink condition should be maintained. The temperature is maintained at 37.5^0C. The drug release studies performed for 8 hrs. The 1ml of sample is withdrawn from the basket and same amount of sample is placed in the basket to maintain the sink conditions. The 6.8 buffer solution is used for the *In-vitro* drug release studies. The medium is about 900ml. The sample is withdrawn and under kept for the analyzing of the absorbance under U.V at 230 nm.

Stability studies:[18]The success of an effective formulation can be evaluated only through stability studies. The prepared Quinidine osmotic pump tablets were placed on plastic tubes containing desiccant and stored at ambient conditions, such as at room temperature, 40±2°c and refrigerator 2-8°c for a period of 30days.

III.RESULTS AND DISCUSSION

Compatibility Study

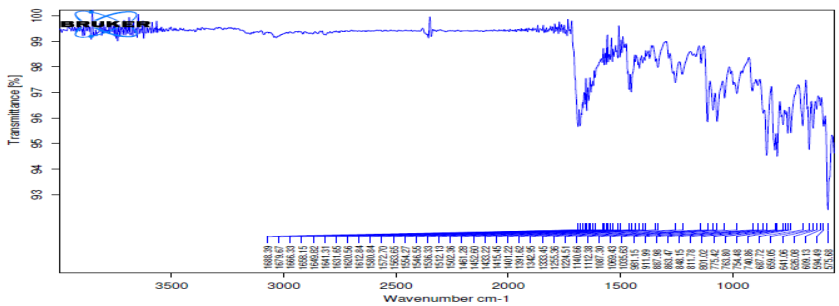

Fig-1: FTIR Studies of Pure drug

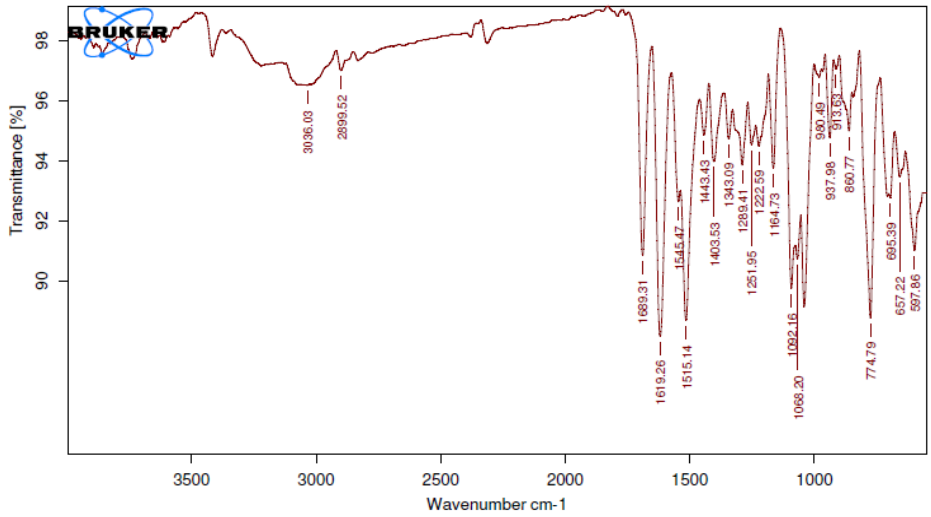

Fig-2: FTIR spectra Optimized formula

Evaluation

Physical Properties of Quinidine:

Interparticulate interactions influence the physical properties of powder flow. A comparison of the bulk density and tapped density can give a measure of the relative importance of this interaction in a given powder. Such a comparison is often used as an index of the ability of the powder to flow.Physical properties of Quinidine like bulk density, tapped density, compressibility index, Hausner's ratio, and angle of repose are given below.

Table-2: Average values of pre-compressive parameters of tablet blend

F.NO	BULK DENSITY	TAPPED DENSITY	COMPRESSIBILITY INDEX	HAUSNERS RATIO	ANGLE OF REPOSE(θ)
F1	0.512	0.611	16.2	1.19	30
F2	0.525	0.615	14.6	1.17	29
F3	0.519	0.625	16.9	1.22	30
F4	0.528	0.623	15.2	1.17	28

Evaluation of Tablets: The tablet formulations were subject to various post-compressive evaluation tests such as, Hardness, Friability and Weight variation, drug content uniformity.

Weight variation test: It was carried out as per official method and the average percentage deviation of all the formulation was found to be within the limit (as per USP standard).

Content uniformity: Was also carried out as per official method and it was found that all batches shows good content uniformity. The values for all the formulations were in the ranges from 89.23-95.85%.

Hardness test: States that all the formulations were found in the range 4to 8 kg.

Friability test: Compressed tablets have lost less than 1 %of their weight is generally considered acceptable. All the formulations have less than 1% friability.

Table-3: Results of Evaluation parameters of tablets

F. No.	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)
F1	300	5.10	4.83	0.52	90.10
F2	299	4.98	4.75	0.50	89.23
F3	300	5.06	4.53	0.63	95.85
F4	400	5.12	4.19	0.55	92.95

The tablets of 4 formulations were tested and analyzed for thickness, weight variation, hardness, friability, content uniformity.

Table-4: Cumulative % of drug release

Time (hrs)	F_1	F_2	F_3	F_4
0	0	0	0	0
1	13.25	18.36	19.65	20.65
2	28.94	29.92	31.85	33.68
3	34.64	37.93	49.25	47.91
4	44.95	44.72	60.92	59.97
5	56.55	55.92	69.90	62.20
6	68.92	68.83	76.15	76.82
7	79.63	80.21	85.98	83.88
8	89.99	91.56	96.25	93.36

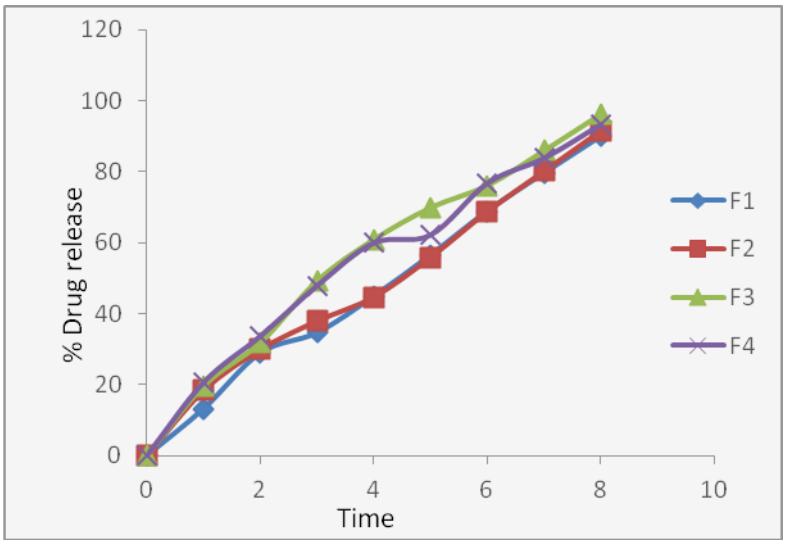

Fig-3: *In-vitro* drug release of all formulations

Stability studies

There was no significant change in physical and chemical properties of the tablets of formulation F-3 after 1 month. Parameters quantified at various time intervals were shown

Table-5: Results of stability studies of optimized formulation F-3

Formulation Code	Parameters	Initial	1st Month	Limits as per Specifications
F-3	25^0C/60%RH % Release	96.25	96.20	Not less than 85 %
F-3	30^0C/75% RH % Release	96.25	96.18	Not less than 85 %
F-3	40^0C/75% RH % Release	96.25	96.13	Not less than 85 %

IV.CONCLUSION

The conclusions drawn from the present investigation are as follows. Extended release formulations of Quinidine were developed based on controlled porosity osmotic pump technology. Core tablets of Quinidine were successfully prepared by direct compression for drug layer using Quinidine, microcrystalline cellulose, sodium chloride, Magnesium stearate. After compression core tablets coated with polymers. *In vitro* release profile of formulation F3 was found to be release profile was found to be 96.25%. Finally the F3 formulation was optimized. The effect of different formulation variable was studied to optimize release profile. Drug release was directly proportional to the pore former, when we increase the concentration of pore former from 30 to 50% along with increase in osmogent ratio, the drug release also found to be increased. Drug release from the developed formulations was found to be independent of Hydrodynamic conditions of the body and depends on pH, because the solubility of the drug is pH dependent.

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