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DESIGN AND CHARACTERIZATION OF QUININE SULFATE MODIFIED RELEASE MINI-TABLETS USING ARTIFICIAL CELLULOSE POLYMERS

DEVI THAMIZHANBAN*, NEHA S AND LAKSHMI K

Chettinad School of Pharmaceutical Sciences, CARE, Tamil Nadu, India - 603 103

***Corresponding Author: Dr. Devi Thamizhanban: E Mail: devit@care.edu.in**

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ABSTRACT

Research work involves in formulation development of a modified release dosage form of Quinine sulfate mini- tablets using cellulosic polymers (Hypromellose) as a release retarding agent for reduction of dosing frequency and patient compliance. The formulation is evaluated by titrating with various concentration of Hypromellose of two different grades, HPMC K4M and HPMC K100LVCR (two different viscosity range of polymers) to achieve the target drug release of loading dose plus maintenance dose. The manufacturing process involves, wet granulation, and followed by compression. The formulation with 10% w/w of HPMC K4M and 5% w/w of K100LVCR was observed with release profile complies with zero order kinetics model. Sustained release matrix can promise better compliance through reduction in over-all dose and dosage regimen, which support to treat continual sickness. The developed formulation can improve the patient compliance and reduces the dosage regimen.

Keywords: Quinine sulfate, Hypromellose, sustained release, mini-tablets

INTRODUCTION:

Quinine sulfate (quinine) has been used as an anti-malarial agent at the beginning. However, advanced and used within the UK for decades to the treatment of nocturnal leg cramps. Muscle cramps are a commonplace symptom, **[1]** affecting patients with and without diabetes. Muscle cramps are defined as involuntary, normally painful contractions of a muscle group and can be common, excessive and disabling.

They may be because of ectopic discharges from nerves and, despite the fact that notion to be exacerbated via metabolic problems, neuropathic conditions, pregnancy, hypomagnesaemia, hypocalcaemia, hypothyroidism, renal and liver disorder are most typically idiopathic. Several capsules generally utilized in diabetes along with lipid decreasing retailers, diuretics, beta-blockers and insulin also are thought to increase chance of cramps. Patients with diabetic neuropathy can revel in muscle cramps, at the side of different symptoms of pain and altered sensation. signs of neuropathy in sufferers with diabetes are a therapeutic challenge and remedy frequently involves multiple treatment options. Sustained release dosage form enables patient compliance by reducing the number of doses intake per day as well as, the reduction in exposure of drug quantity to the body **[2-4]**.

Modified release formulations are designed using Hypromellose, for forming a hydrogel matrix, which allows the drug release in diffusion mechanism. Different viscosity ranges and viscosity grades of Hypromellose available for achieving various gel strength and release mechanism **[5, 6]**.

MATERIALS AND METHODS:

Quinine sulfate, HPMC K4M (Hydroxy propyl methyl cellulose), HPMC K100M, PVP (Poly vinyl pyrrolidone) K30, Lactose Anhydrous, Isopropyl Alcohol, Magnesium Stearate and Talc.

Quinine sulfate, lactose anhydrous, Hypomellose K4M and Hypromellose K100LVCR are passed though ASTM (American standard test mesh) 20#, mixed in a planetary mixer. Different ratios of Hypromellose with both grades were evaluated for achieving the release profile **[7]**. Povidone K-30 was dissolved in isopropyl alcohol and used as binder solution for granulation. The binder solution was added to the planetary mixer, mixed for 5 minutes, and the wet mass was dried using tray drier at 50 ± 5 °C, till to achieve the LOD of NMT 2.0%. The dried granules were passed though ASTM 30#. Talc and magnesium stearate were sifted through ASTM 40#, mixed with dried granules for 5 minutes. The blend was compressed into mini tablets using 6.0mm, circular standard concave punch, with the target weight of 100mg.

Table 1: Unit formula of Sustained Release Quinine Sulfate Tablet 400mg

S. No.	Ingredients	Qty (mg/unit)				
		Trial -1	Trial -2	Trial -3	Trial -4	Trial -5
1	Quinine Sulfate	400	400	400	400	400
2	Hypromellose K4M	50	40	60	40	30
3	Hypromellose K100 LVCR	30	40	0	20	30
4	Lactose Anhydrous	29	29	49	49	49
5	Povidone K-3	30	30	30	30	30
6	Isopropyl alcohol	qs	qs	qs	qs	qs
7	Talc	5.5	5.5	5.5	5.5	5.5
8	Magnesium stearate	5.5	5.5	5.5	5.5	5.5
		550	550	550	550	550

Figure 1: Rotary tablet compression machine

Figure 2: Quinine Sulfate Sustained Release Mini Tablets

The formulated tablets were evaluated for physical and chemical characterisation, observed with the following results

Tablet Hardness: Three tablets were randomly selected from each batch and tested using a Pfizer hardness tester. The percentage deviation was calculated.

Uniformity of Weight: Weight change test Average weight was determined by taking twenty tablets that were weighed

individually and collectively. Weight gain was calculated and weight change was examined.

% of weight Variation = average wt.– average wt. individual wt. / average wt×100

Friability Test: Friability test was performed as per European Pharmacopoeia (EP 6.0). Test was performed using Roche friability tester, the drum was rotated at 25 rpm for 4 min. Sample of whole tablets corresponding as near as possible to 6.5 g was taken. Accurately weighed tablet sample was placed in the drum. The drum was rotated for 100 times, and removed the tablets. Removed any loose dust from the tablets as before, and accurately weighed.

Calculate and analyzethe percentage o f variancefor friability testing. Calculate the friability percentage for each batch using t he formula below:

Percentage friability = (initial weight-final weight/initial weight) × 100

Tablet Thickness: Take five tablets and measure their thickness with Vernier caliper. Thickness is measured by placing the concave surface of tablets between the two arms of caliper.

Dissolution Studies: 5 units of mini tablets of quinine sulfate extended release tablets were loaded in to each dissolution vessel. The drug was released from Quinine sulfate tablets *in-vitro* using a paddle tablet dissolution apparatus containing 900 ml of dissolution medium maintained at 37 ± 5 °C with a stirring speed of 50rpm.

For the first 2 hours, 0.1N HCl was used as dissolution medium, followed by the dissolution medium was changed to pH 7.2 phosphate buffer for 6 hrs. At the beginning of the period, 10ml solution was analysed spectrophotometrically at 329 nm. For each sample 10ml of fresh sample was replaced, for maintaining the dissolution volume of 900ml **[8, 9]**.

RESULTS AND DISCUSSION:

The physical parameter reveals all the trial formulation complies with the physical parameters. Hence, the all the trial formulations were evaluated for in-vitro characterisation. A cumulative percentage drug release of Quinine sulfate tablets with zero order kinetics compliance is presented in **Table 3 [11, 12]**.

The dissolution profile for all the 5 trial formulation results were evaluated for first order kinetics, and presented below in **Table 4 [13]**.

Table 2: Physical Parameters of Quinine Sulfate Sustained Release Mini Tablets

Parameters [10]	Trial -1	Trial -2	Trial -3	Trial -4	Trial -5
Thickness (mm)	3.2 ± 0.2mm	3.1 ± 0.2mm	3.1 ± 0.2mm	3.2 ± 0.3mm	3.3 ± 0.2mm
Hardness (N)	60-80N	50-80N	65-90N	55-75N	60-80N
Friability (% w/w)	0.65	0.43	0.25	0.52	0.24
Weight variation (mg)	112 ± 4mg	111 ± 5mg	113 ± 3mg	112 ± 4mg	110 ± 5mg

Table 3: Cumulative percentage drug release Vs time (zero order rate kinetics)

Trial	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5
Time (hrs)	1	2	3	4	5
0	0	0	0	0	0
1	24	33	16	20	18
2	36	55	28	36	42
3	55	71	48	50	55
4	71	85	67	64	78
6	82	98	82	85	98
8	98	99	98	99	99
Slope	11.87	11.82	12.53	12.29	13.03
R sqr	0.951	0.849	0.959	0.979	0.892
y Intercept	11.60479	22.47305	5.479042	8.443114	11.02994

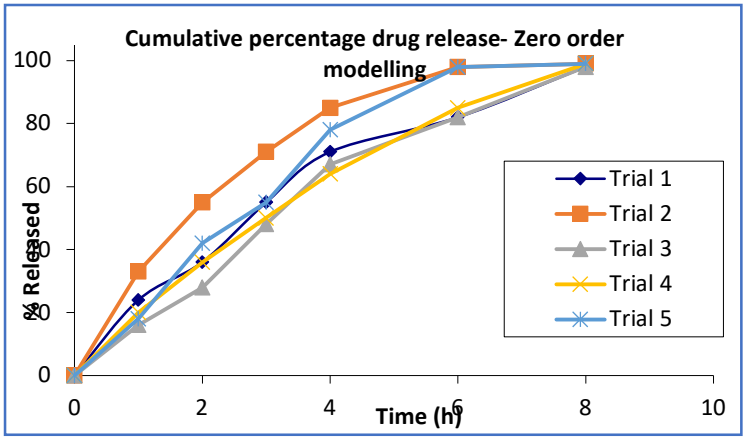

Figure 3: Dissolution profile of Quinine Sulfate sustained Release tablets

Table 4: Cumulative percentage first order release (Time Vs log % remained)

Trial	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5
Time (hrs)	1	2	3	4	5
0	4.61	4.61	4.61	4.61	4.61
1	4.33	4.20	4.43	4.38	4.41
2	4.16	3.81	4.28	4.16	4.06
3	3.81	3.37	3.95	3.91	3.81
4	3.37	2.71	3.50	3.58	3.09
6	2.89	0.69	2.89	2.71	0.69
8	0.69	0.00	0.69	0.00	0.00
R sqr	0.899	0.973	0.905	0.873	0.951
y Intercept	4.941893	4.89278	5.040834	5.134789	5.134487
Slope	-0.45	-0.62	-0.46	-0.52	-0.64

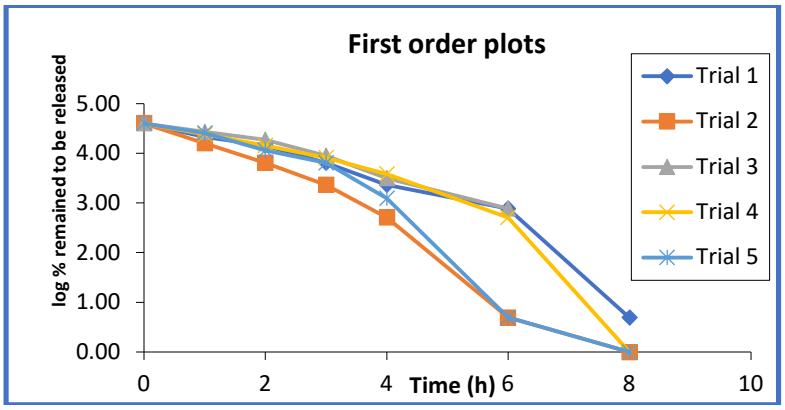

Figure 4: First order kinetic interpretation of Quinine sulfate Sustained release tablets

CONCLUSION:

In this phase of the study, various evaluation factors that are being affecting the output were analyzed. The wet granulation method was developed. Tablets were tested for Physical parameters of weight variation, Hardness, thickness and friability. The *in-vitro* dissolution performed indicates the trial 2 is closer towards first order kinetics release profile and trial-4 is closer to zero order kinetics release profile. As zero order is most preferred kinetic profile for sustained release dosage form, the same shall be used for subsequent studies.

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