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Hydrophilic polymers as release modifiers for primaquine phosphate: Effect of polymeric dispersion

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ABSTRACT

Primaquine (PQ), a synthetic compound with potent antimalarial activity is characterized by low plasma half life, requiring frequent administration leading to several undesired side effects, patient incompliance. The objective of the present study was to design an extended release formulation incorporating PQ in hydrophillic matrix composed of HPMC,Sodium CMC, Sodium alginate. Effects of polymeric dispersions of ethyl cellulose (EC) and polyvinylpyrrolidone (PVP) was also studied. Tablets were prepared by wet granulation method. The results of angle of repose (<30) and compressiblity index (upto 15%) indicate good flow properties. Tablets were subjected to weight variation, hardness, friability and drug content tests. The swelling and drug release profile were investigated under dissolution condition. The result showed that the swelling index & release retarding capacity follows HPMC>Sodium CMC>Sodium alginate, which was further sustained by polymeric dispersions of EC and PVP. The kinetics of drugs showed extended release of up to 20 hrs (F3) following non fickian diffusion (0.45<n<0.89).

KEY WORDS: Primaquine phosphate, Extended release tablets, Hydroxypropylmethylcllulose, Sodium CMC, Sodium alginate, Fickian

RESUMEN

La primaquina (PQ), un compuesto sintético con actividad antimalaria fuerte, se caracteriza por tener una vida media de plasma baja, lo que requiere una administración frecuente y provoca varios efectos colaterales no deseados, con inconformidad del paciente. El objetivo del estudio actual fue diseñar una formulación de liberación prolongada que incorpora PQ en una matriz hidrofílica compuesta de HPMC, CMC de sodio y alginato de sodio. Se estudiaron también los efectos de las dispersiones poliméricas de etilcelulosa (EC) y polivinilpirrolidona (PVP). Los comprimidos se prepararon según el método de granulación húmeda. Los resultados de la respuesta de ángulo (<30) y el índice de compresibilidad (hasta el 15%) mostraron propiedades de flujo buenas. Los comprimidos se sometieron a pruebas de variación de peso, dureza, friabilidad y contenido de fármaco. La hinchazón y el perfil de liberación del fármaco se investigaron bajo condiciones de disolución. Los resultados mostraron que el índice de inflamación y la capacidad retardada de liberación son mayores con HPMC que con CMC de sodio, y que estos a su vez son mayores que con alginato de sodio, los cuales fueron más sostenidos por dispersiones poliméricas de EC y PVC. La cinética de los fármacos mostró una liberación prolongada de hasta 20 horas (F3) siguiendo una difusión no de Fick (0,45<n<0,89).

PALABRAS CLAVE: Fosfato de primaquina, Comprimidos de liberación prolongada, Hidroxipropilmetilcelulosa, CMC de sodio, Alginato de sodio, Fickian.

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INTRODUCTION

Primaquine phosphate, 8-[(4-amino-1-methyl butyl) amino]-6-metoxyquinoline phosphate, a synthetic compound with potent antimalarial activity is considered to be a prominent medicine against resurgence and is also prescribed for terminal prophylaxis. It shows a broad spectrum activity against various stages of parasite, particularly asexual hepatic stages and latent tissue forms. It is removed rapidly from blood. Excretion metabolism, or tissue localization account for rapid elimination of primaquine from the plasma[1]. PQ is also characterized by low plasma half-lives of 4-5 hrs[2,3], which require frequent administration and amplify its adverse effects[4] . The clinical use of primaquine for long period and repeated oral dosing can cause nausea, abdominal pain and oxidant haemolysis with methemoglobinemia, anemia, haemoglobinurea and is contraindicated in patients with different variants of glucose-6-phosphate dehydrogenase deficiency[5]. Moreover it may cause poor patient compliance leading to sub therapeutic primaquine concentration in plasma, promoting drug resistance[6]. In order to improve the therapeutic efficacy of the drug and diminish its toxicity, various approaches have been examined such as nanoparticulate system[7], albumin carrier protiens[8], nanoemulsions[9] transdermal patches[10]. Some researchers have proposed high dose over short administration periods but PQ at high doses may affect gene expression in liver and produce undesirable outcomes if administered over long time periods[11]. Recently many controlled release formulation based on matrix system have been developed. These delivery systems are characterized by controlled release of the drug thereby reducing frequency of dosing & hence decreasing fluctuation of plasma levels to obtain better therapeutic effects with reduced toxicity.

Hydrophilic matrices are commonly used as oral drug delivery systems and being increasingly investigated for development of controlled release drug delivery system owing to compatibility, availability and economy. The release properties of matrix system may be dependent upon the solubility of the drug in the polymer matrix or in case of porous matrices, the solubility in the sink solution within the particles pore network[12]. Hydrophilic matrix gradually begins to hydrate from the periphery towards the centre forming a gelatinous swollen mass which controls the diffusion of drug molecules through polymeric materials into aqueous medium. Penetration by the solvent produces a clearly defined front at interface between the dry and hydrated form. The thickness of the hydrated gel layer determines the diffusional path length of the drug. Hence it can be optimized that if mechanism of release follows fickian diffusion, then rate will follow higuchi equation:

$$Q=(2ADC_s t)^{1/2} \qquad (1)$$

However, diffusion is generally not the only mechanism controlling the release. It has been reported that in aqueous medium the polymer undergoes relaxation process resulting in slow erosion of the hydrated polymer envisaging that both the mechanism may work simultaneously contributing to the overall release rate[13] Hydroxy propyl methyl cellulose (HPMC) is the dominant hydrophilic vehicle used for the preparation of oral controlled drug delivery systems[14] The transport phenomena involved in the drug release from hydrophilic matrices are complex because the microstructure and macrostructure of HPMC exposed to water is strongly time dependent. When it comes in contact with the gastrointestinal fluid, HPMC swells, gels, and finally dissolves slowly. The gel becomes a viscous layer acting as a protective barrier to both the influx of water and the efflux of the drug in solution. Numerous studies have been reported in literature investigating the HPMC matrices to control the release of a variety of drugs[15,16]. Sodium alginate have also been reported as release retarding agent as hydration of an alginate matrix leads to a formation of gelatinous layer which acts act as a diffusion barrier[17]. Sodium carboxy methyl cellulose (Sodium CMC) have also been explored as release modifiers as it characterizes the properties of hydrophilic polymers[18]. Efforts were made to gain optimum zero order release, hence present study investigates the feasibility of incorporating polymeric solution of ethyl cellulose (EC) and polyvinyl pyrrolidone (PVP) into primaquine controlled release matrix system and to carry out In vitro investigation.

MATERIALS AND METHODS

Primaquine phosphate was supplied as gift sample from central drug research institute (Lucknow, India). HPMC, Polyvinyl pyrrolidone (PVP) K90 was procured from Himedia (Mumbai,India). Ethyl cellulose was procured from (Merck, India). All other ingredients used throughout the study were of IP grade and were used as received.

Preparation of sustained release matrix tablets:

Matrix tablets were prepared by wet granulation method. The composition of various formulations is given in table 1. PQ and HPMC were mixed in a polybag, and the mixture was passed through mesh (No. 40). Granulation was done using 4% solution of PVP & 8% solution of ethylcellulose in isopropyl alcohol. After enough cohesiveness was obtained the mass was extruded through mesh no 10. The wet granules were air dried for 4 hours thereafter kept in a desiccator for 12 hours at room temperature for complete removal of alcohol. The granules were then sized by mesh No. 16 and mixed with talc and magnesium stearate as glidant and lubricant respectively. Tablets were

Table 1. Hydrophilic matrix tablet composition (mg)									
Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug	50	50	50	50	50	50	50	50	50
HPMC	50	50	50	---	---	---	---	---	---
Na CMC				50	50	50	---	---	---
Na alginate							50	50	50
Pvp(4%)	---	q.s	---	---	q.s	---	---	q.s	---
Ec(8%)	---	---	q.s	---	---	q.s	---	---	q.s
Mg stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Talc upto	200	200	200	200	200	200	200	200	200

compressed at 200 mg weight on a single station tableting machine (Cadmach, India) with 9-mm biconvex punches. Nine different formulas were developed to evaluate the drug release and to study the effect of auxiliary substance on drug release.

Evaluation of granules

Angle of Repose: The angle of repose of granules was determined by the funnel method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted such that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the graph paper placed on the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation[7].

$$\tan \theta = h/r \qquad (2)$$

Where, h and r are the height and radius of the powder cone respectively.

Bulk Density: A quantity of 2 g of powder from each individual formula, shaken lightly to break any agglomerates formed and was introduced into a 10-mL measuring cylinder, Initial volume was observed, further cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2- second intervals. The tapping was continued until no further change in volume was noted. Loose bulk density (LBD) and tapped bulk density (TBD) were calculated using the following formulae[8]:

LBD=weight of the powder/volume of the packing (3)

TBD= weight of the powder/tapped volume of the packing (4)

Where, LBD= Loose bulk density; TBD= Tapped bulk density.

Compressibility Index: The compressibility index of the granules was determined by Carr's compressibility index[9] Compressibility index was determined by the same instrument as used for bulk density determination.

Carr´s Index (%)= [(TBD-LBD) x100]/TBD (5)

Total Porosity: Total porosity was determined by measuring the volume occupied by a selected weight of a powder (Vbulk) and the true volume of granules (the space occupied by the powder exclusive of spaces greater than the intermolecular space)[10].

Porosity (%)= (Vbulk -V)/Vbulk x100 (6)

Drug Content: An accurately weighed amount of powdered primaquine phosphate granules (100 mg) was extracted with water and the solution was filtered. The absorbance was measured at 222 nm after suitable dilution.

Evaluation of Tablets

Weight Variation Test: To study weight variation, 20 tablets of each formulation were weighed using an electronic balance (Denver, Germany) and the test was performed according to the official method.

Swelling Behavior of Tablets: The extent of swelling was measured in terms of percentage weight gain by the tablets. The swelling behavior of all the formulations was studied. Three tablets from each formulation was kept in Petri dish containing phosphate buffer pH 6.8. At the end of 2, 4, 6, 8, 10 and 12hrs tablets were withdrawn, soaked on tissue paper and weighed, and then percentage weight gain by the tablet was calculated using formula.

$$SI = Mt - \frac{Mo}{Mo} \times 100 \qquad (7)$$

Where, SI = Swelling index, Mt = Weight of tablet at time 't' and Mo = Weight of tablet at time '0'.

Drug Content: Five tablets were weighed individually, and the drug was extracted by vortexing in water. The drug content was determined spectrophotometrically at 222 nm (Shimadzu, 1707).

Hardness and Friability: The hardness (n=6) and friability (n=20) of tablets of each batch, were determined using the MONSANTO Hardness tester and the Friability test apparatus (Lab India, Mumbai, India), respectively.

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Invitro Release Studies: Drug release was assessed by dissolution test under the following conditions: n = 6 (in triplicate), USP type II dissolution apparatus (Lab India, Mumbai, India) at 50 rpm in 900 mL of phosphate buffer at pH 7.4 maintained at 37°C ± 0.5°C. Ten milliliters of the sample was withdrawn at regular intervals and replaced with the same volume of prewarmed (37°C ± 0.5°C) fresh dissolution medium. The samples withdrawn were filtered through whatman filter paper. The drug release at different time intervals was measured by UV-visible spectrophotometer (Shimadzu 1701, Japan) at 222 nm.

Study of Release Kinetics: In order to investigate the mode of release from tablets, the release data was analyzed with the following mathematical models:

Zero order equation; $(Q = K_{0t})$ (8)

First order equation; $[In (100-Q) = In Q-K1_t]$ (9)

Higuchi equation; $(Q=kt^{1/2})$ (10)

Korsmeyer and peppas equation;$(Q= kpt^n)$ (11)

Where Q is the percent of the drug release at time t,k0 and kt are the coefficients of equation. kp is constant incorporating structural and geometric characteristics of the release device and n is the release exponent indicate the release mechanism.

Hixson-Crowell cube root law; $(Q_0^{1/3}-Q_t^{1/3}=K_{hc} t)$ (12)

Where, Q_t is the amount of drug released in time t, Q_0 is the initial amount of the drug in tablet and Khc is the rate constant for Hixson-Crowell rate equation.

RESULTS AND DISCUSSION

Evaluation of granules:

A granule is an aggregation of component particles that is held together by the presence of bonds of finite strength. Physical properties of granules such as specific surface area, shape, hardness, surface characteristics, and size can significantly affect the rate of dissolution of drugs contained in a heterogeneous formulation. The results of angle of repose (<30) indicate good flow properties of the granules. This was further supported by lower compressibility index values. Generally, compressibility index up to 15% result indicates good to excellent flow properties. The drug content in a weighed amount of granules of all formulations range as specified in IP. The percentage porosity values of the granules ranged from 26.92% to 34.25%, indicating close to lose packing, which further confirms uniform size of particles Generally, a percentage porosity value below 26% shows that the particles in the powders are of greatly different sizes and a value greater than 48% shows that particles exist as aggregates or flocculates (table 2).

Evaluation of tablets:

Direct compression is the preferred technique for making controlled release tablet formulations. However, study shows that when the tablet contains water soluble active substance , direct compression technique would be less effective[19]. PQ is a water-soluble, hydrophilic material, which allows quicker penetration of water in the system, resulting in rapid release. This characteristic release had been controlled by hydrophilic polymers such as HPMC, Sodium CMC and Sodium alginate in the system and further adopting aqueous granulation for making tablets. The results of the uniformity of weight, hardness, drug content, thickness, and friability of the tablets are depicted in table 2. All the samples of the test product complied with the official requirements for uniformity of weight. The drug content was found to be equivalent as label claim for PQ in all formulations. The low friability (less than 1%) indicates that the matrix tablets were compact and hard. The results were reproducible, even on tablets that had been stored for about 90 days at room temperature and 70% relative humidity (table 3).

Swelling behavior of tablets:

Since hydrophilic matrices control the release through diffusion and erosion process by forming a gelatinous swollen mass, the rate of swelling and erosion is related and may also affect the mechanism and kinetics of drug release. The penetration of the dissolution medium in the hydrated tablets was determined. The swelling index of tablet at various time intervals was plotted as shown in figures 1. The swelling behavior followed the following sequence HPMC>Sodium CMC> Sodium alginate. Due to high swelling index HPMC could sustain the release rate more than Sodium CMC and sodium alginate. The swelling of polymers were characterized by anisotropic swelling phenomenon (i.e more swelling in the axial direction than in the radial direction on exposure to water). The reason for such preferential swelling in an axial direction must be due to the need for the directional stresses, imposed on polymers during tableting, to relax. The swelling capacity was sustained due to the presence polymeric dispersions of PVP & ethyl cellulose as it delays erosion process hence making the tablets remain intact and further sustaining drug release. This delay in erosion process might be due low solubility of PVP and EC as compared to polymer matrix.

Invitro Release Studies

The invitro drug release characteristics were studied in Phosphate buffer pH 7.4 for a period of 24 hours using USP Type II dissolution apparatus at 50 rpm. Figure 2 shows that the retarding capacity follows HPMC>Sodium CMC>Sodium alginate. Tablets containing HPMC (F1),

Table 2. Evaluation of granules.

Ingredients	Angle of repose (n=3)	Loose bulk density (g/ml) (n=3)	Tapped bulk density (g/ml) (n=3)	Compressibility index (%) (n=3)	Total porosity (%) (n=3)	Drug content (%) (n=3)
F1	24.68±0.02	0.396±0.03	0.445±0.06	11.01±0.03	34.25±0.03	97.68±0.06
F2	23.97±0.08	0.267±0.02	0.301±0.03	11.29±0.01	33.09±0.07	98.41±0.01
F3	22.73±0.04	0.407±0.05	0.485±0.05	14.08±0.02	27.21±0.02	98.62±0.03
F4	21.84±0.03	0.312±0.02	0.364±0.01	14.28±0.04	31.42±0.01	96.64±0.04
F5	23.91±0.01	0.338±0.07	0.385±0.02	12.20±0.05	28.43±0.03	98.14±0.05
F6	24.11±0.07	0.421±0.03	0.481±0.07	12.47±0.03	26.92±0.06	95.53±0.02
F7	23.95±0.02	0.219±0.04	0.248±0.03	11.69±0.02	31.74±0.04	97.77±0.01
F8	22.01±0.06	0.298±0.08	0.342±0.02	12.86±0.02	32.03±0.02	96.01±0.04
F9	22.13±0.09	0.347±0.04	0.412±0.08	15.77±0.01	30.08±0.06	97.05±0.02

Table 3. Physical evaluation of tablets.

Ingredients	Hardness (kg/cm²) (n=6)	Friability (%) (n=20)	Weight variation (%) (n=20)	Drug content (%) (n=6)
F1	4.0±0.12	0.69±0.02	3.24±0.06	98.45±0.04
F2	4.2±0.81	0.78±0.04	2.45±0.02	99.89±0.56
F3	4.8±0.04	0.76±0.01	2.09±0.08	99.25±0.23
F4	4.5±0.23	0.71±0.06	3.00±0.05	100.93±0.45
F5	4.6±0.63	0.68±0.05	2.54±0.01	101.12±0.67
F6	4.0±0.21	0.85±0.03	2.16±0.04	98.81±0.78
F7	4.5±0.18	0.76±0.02	2.98±0.01	99.12±0.34
F8	4.5±0.23	0.88±0.01	2.68±0.02	99.68±0.34
F9	4.6±0.05	0.81±0.04	2.98±0.05	99.89±0.25

Sodium CMC (F4) & Sodium alginate (F7) approx 90% drug release after 10,6 & 5 hrs respectively. Prolonged release for HPMC was observed as it may due to more viscous solution. Formulations F4 & F7 underwent erosion before complete swelling could take place, resulting in faster release of drug. The release of the drug was further sustained by the addition of polymeric dispersions of PVP & ethyl cellulose as it delays erosion of polymers. F3 formulation showed maximum retention and released 98% of the drug in 20 hrs.

Study of Release Kinetics:

In order to determine the release model which best describes the mechanism of drug release, the in vitro release data were fitted to zero order, first order and diffusion controlled release mechanisms according to the simplified higuchi model (cumulative percentage of drug released vs. square root of time). The release pattern of a certain mechanism was based on the correlation coefficient (r) for the parameters studied, where the highest correlation coefficient is preferred for the selection of mechanism of release. Successive substantiation of the relative legality of diffusion and first order models obtained by analyzing the data using the following equation of korsmeyer and
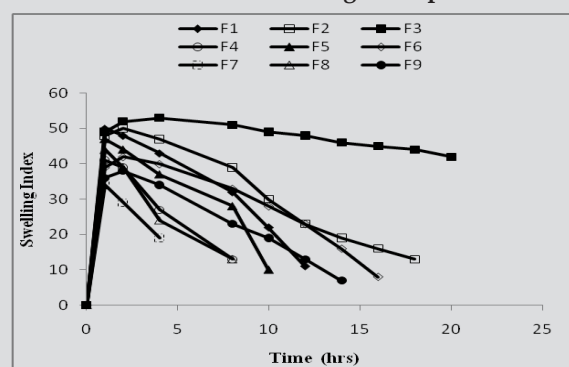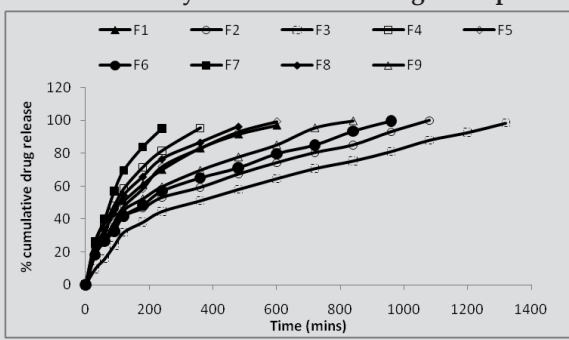

Figure 1. Swelling behavior of polymers under dissolution conditions. Readings in triplicate.

Figure 2. Release profile of PQ from tablets prepared by HPMC, Sodium CMC, Sodium alginate and effect of other auxiliary substances. Readings in triplicate.

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Table 4. Kinetic values obtained from different plots of formulations, F1 to F9.

Ingredients	First order	Zero order	Higuchi	Korsmeyer-peppas		Hixson crowell
	R^2	R^2	R^2	R^2	n	R^2
F1	0.898	0.988	0.988	0.98	0.51	0.988
F2	0.956	0.957	0.957	0.99	0.52	0.981
F3	0.948	0.954	0.954	0.97	0.56	0.991
F4	0.942	0.996	0.996	0.99	0.53	0.992
F5	0.914	0.990	0.990	0.98	0.57	0.993
F6	0.940	0.960	0.962	0.99	0.47	0.983
F7	0.948	0.991	0.991	0.98	0.64	0.993
F8	0.910	0.998	0.998	0.98	0.53	0.995
F9	0.932	0.904	0.989	0.98	0.49	0.970

peppas (log cumulative percentage of drug released vs. log time)
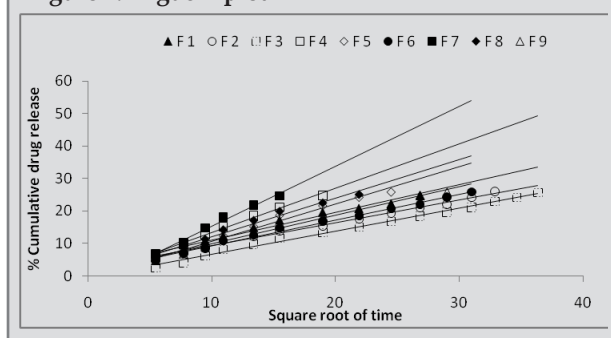
$$Mt - M^\infty = k.t^n \tag{13}$$

Where, Mt/M^∞ is the fraction released by the drug at time t, K is a constant incorporating structural and geometric characteristic and n is the release exponent characteristic for the drug transport mechanism. Value of n=0.45 indicates a classical fickian diffusion controlled drug release and the release rate is dependent on t, while 0.45< n <0.89 indicate anomalous (drug diffusion in the hydrated matrix and the polymer relaxation) transport and when n = 0.89, the release is zero order, non fickian, indicates a case II relaxational release transport. The data were also plotted according the hixson crowell cube root law to examine the effect of surface area on the release mechanism.

In our experiments, the in vitro release profiles of drug from all the formulations could be best expressed by higuchi's equation, as the plots (Figure 3) showed high linearity (R^2: 0.954 to 0.998). Higuchi model has been used to explain release of water soluble or insoluble drug from solid matrix. Higuchi equation is followed usually when the release follows diffusion mechanism. To confirm the diffusion mechanism, the data were fit into korsmeyer peppas model. All formulations F-1 to F-9 showed high linearity (R^2: 0.977 to 0.995), with slope (n) values ranging from 0.47 to 0.64, which indicates drug release mechanisms involving a combination of both diffusion and chain relaxation mechanisms. The dissolution data were also plotted in accordance with hixson crowell cube root law, applicability of data (R^2 = 0.970 to 0.995) indicates a change in surface area and diameter of tablets with the progressive dissolution of matrix as a function of time (table 4).

CONCLUSION:

In this study, hydrophilic matrix tablets composed of HPMC, Sodium CMC & sodium alginate containing hydrophilic drug primaquine were prepared. HPMC,

Figure 4: Higuchi plot

Sodium CMC & sodium alginate were chosen as release modifiers as they exhibit the property of gelation polymer. Effect of ethanolic solution of PVP & ethyl cellulose was also investigated. The release rates for primaquine from formulation containing HPMC matrix was significantly retarded as compared to other polymer matrices. The release was further retarded by the addition of ethanolic solution of PVP & ethylcellulose as they act as binder and lead to a formation of stiffer matrix which prevent erosion of the polymer, prominently releasing the drug by diffusion process.

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