WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES
SJIF Impact Factor 6.041
Volume 5, Issue 11, 719-727 Research Article ISSN 2278 – 4357

FORMULATION AND EVALUATION OF SUSPENSION CONTAINING CHLOROQUINE SULPHATE-LOADED EUDRAGIT EPO MICROSPHERES

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Article Received on
05 Sept. 2016,

Revised on 25 Sept. 2016,
Accepted on 15 Oct. 2016

DOI: 10.20959/wjpps201611-7364

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ABSTRACT

The objective of this work was to develop and evaluate suspension of taste masked microspheres of chloroquine sulphate. The microspheres were prepared by the solvent evaporation technique using pH sensitive polymer Eudragit EPO. Guar gum was used as suspending agent. Prepared suspension formulations were tested for sedimentation rate, *in vitro* drug release and taste masking. This result indicated that no leakage of drug occurred from the microspheres in the suspension on storage. Moreover the same release rate of chloroquine sulphate from the microspheres suspension and microspheres alone, indicated that the suspension medium studied did not affect the property of drug release. Thus, results conclusively demonstrated successful taste masking and formulation of suspension with taste masked microsphere especially for pediatric patients.

KEYWORDS: Chloroquine sulphate, taste masked microspheres, suspension, in vitro drug release profile.

INTRODUCTION

Taste can be defined as chemical reaction derived from sensory responses from the four main taste perceptions: salt, sour, bitter and sweet. Taste sensation is the result of signal transduction from the receptor organs for taste, commonly known as taste buds. The taste buds contain very sensitive nerve endings which produce and transmit electrical impulses to the brain. The perception of taste only occurs when the substances are dissolved. The drug

substance first gets solubilized in saliva, then they interact with taste buds and perception of taste occurs.[1] The bitterness of pharmaceutical drug plays a critical role in patient compliance as the oral administration of bitter drugs is often hampered by their unpleasant taste, leading to noncompliance and thus decreasing therapeutic efficacy, especially in case of children and the elderly. So masking of bitter pharmaceuticals is very important.[2]

The present work involved masking the bitter taste of chloroquine sulphate by microencapsulating the drug with pH sensitive polymer Eudragit EPO and formulating into a suspension. The developed taste masked suspension can be a promising approach for enhancing patient compliance especially for pediatric patients and assure the success of therapy.[3]

MATERIAL AND METHODS

Material: Chloroquine Sulphate was procured from Loba Chemicals Mumbai. Eudragit EPO was gifted from Degussa India Pvt. Ltd., Mumbai (India). Magnesium stearate and guar gum was purchased from Loba Chemicals, Mumbai.

Preparation of microsphere

Chloroquine sulphate microspheres were prepared by solvent evaporation technique as described by Biswal et al, 2011. Eudragit EPO was used as the coating polymer.[4] Magnesium stearate was added to the formulation to prevent aggregation of microspheres during solvent evaporation.[5] Liquid paraffin was selected as outer phase since Eudragit EPO is very slightly soluble in it.[6] Acetone has a dielectric constant of 20.7 and was therefore chosen as the dispersed or inner phase since solvents with dielectric constants between 10 and 40 shows poor miscibility with liquid paraffin.[7] The polymer Eudragit EPO was dissolved in 10 ml of acetone to get a clear solution. Chloroquine sulphate and magnesium stearate (40 mg) were added to this mixture and was stirred at the same speed for 30 minutes and then it was kept in the ultrasonic bath until dispersed completely. The resultant dispersion was then poured into a 250 ml beaker containing 150 ml of light liquid paraffin while stirring continuous with a mechanical stirrer at different rpm. Stirring was continued for 3 hours till complete evaporation of acetone. Then the resulted microspheres were collected by filtration under vacuum, washed 4–5 times with 30 ml n-hexane and dried at room temperature (25 °C) for 24 h to get free flowing microspheres.

From the different microsphere formulation variables used, a formulation with optimum characteristics was chosen to prepare suspension formulation.

Method of preparation of suspension

Simple Syrup IP was used as dispersion medium for the suspension. Syrup was prepared by dissolving sucrose in sufficient quantity of warm water and finally required weight was made up. Methyl and propyl paraben were added in the syrup. Guar gum was mixed with 2 ml of water and added to the dispersion medium. Chloroquine sulphate microspheres was added into syrup solution along with polysorbate 80 and was stirred for 30 mins to allow proper dispersion of microspheres. Colouring agent was dissolved in water and transferred to above mixture. Flavouring agent was added and stirred for 5 min. Finally volume was made upto 30ml with distilled water and pH was adjusted to 6.8-7 with sodium citrate solution (1%) as shown in table 1.[8]

Table 1: Formulation code

Sr. no	Ingredients	A1(gm)	A2(gm)	A3(gm)
1	Chloroquine sulphate microspheres equivalent to dose	0.360	0.360	0.360
2	Sugar	18	18	18
3	Methyl Paraben	0.15	0.15	0.15
4	Propyl Paraben	0.08	0.08	0.08
5	Guar gum	0.2	0.3	0.4
6	Polysorbate 80	0.15	0.15	0.15
7	Orange Flavour	0.19	0.19	0.19
8	Distilled water	Up to 30ml	Up to 30ml	Up to 30ml

Evaluation

Threshold bitterness concentration of Chloroquine Sulphate

A panel of seven healthy human volunteers (age 20-25) was selected for the study from whom written consent was obtained. A series of solutions of chloroquine sulphate of concentrations 10, 20, 30, 40 and 50 µg/ml was prepared. The volunteers were asked to taste and rate on the scale from 0 to 4 where 0 meant no bitterness and 4 was for extreme bitter taste. Based on the opinion of the volunteers, threshold bitterness concentration of drug was determined.[9]

Scanning electron microscopy analysis

The shape and surface morphology of microspheres were investigated by scanning electron microscopy (SEM)

Viscosity

The viscosity of suspension was determined at ambient condition using DV III+, Brookfield Programmable Rheometer. In adapter 15ml of suspension was taken and the adapter is set over the viscometer by a stand such a way that spindle is completely immersed in the suspension to measure the viscosity.[10]

Sedimentation Volume

30 ml each of suspension was taken in 50 ml measuring cylinder. The suspension was dispersed thoroughly by moving upside down for three times. Later, the suspension was allowed to settle for three minutes and the volume of sediment was noted. This is the original volume of sediment (Ho).The cylinder was kept undisturbed for 7 days. The volume of sediment read at a fixed time everyday for 7 days was considered as final volume of sediment (Hu).

Sedimentation Volume (F) = Hu/ Ho

The ultimate height of the solid phase after settling depends on the concentration of solid and the particle size.

Redispersibility

The redispersibility of a suspension was evaluated qualitatively. The test consisted of manually shaking the cylinder after the sedimentation experiments were completed. Based on the time and the effort required to convert the sediment to homogenous suspension, the formulations were evaluated. One inversion was considered as 100% easy to be redispersed. Every additional inversion decreased the percent ease of redispersibility by 5%.[11]

In vitro taste evaluation

A quantity of suspension equivalent to therapeutic dose of drug was added to each of the 3 volumetric flasks containing 10 ml of phosphate buffer of pH 6.8. The mixtures were vortexed for 30 and 60 seconds. Content of chloroquine sulphate in each filtrate was determined. For satisfactory taste masking, the amount of drug dissolved at the end of 60 seconds should not be more than the threshold bitterness concentration of the drug.[12]

Table 2: Determination of threshold bitterness of Chloroquine Sulphate

Volunteer no	Rating on the scale of bitterness				
	10ug/ml	20ug/ml	30ug/ml	40ug/ml	50ug/ml
1	0	0	0	1	1
2	0	0	0	1	2
3	0	0	0	2	2
4	0	0	0	1	3
5	0	0	0	1	1
6	0	0	0	1	2
7	0	0	0	2	2

0: no bitterness, 1: threshold bitterness, 2: bitter, 3: moderate bitterness and 4: strong bitterness.

In vitro release study

Drug release tests on the suspension of microspheres were carried out using the paddle method specified in USP XXVII. A suspension sample was quantitatively transferred to the vessel bottom using a syringe. Paddle speed and bath temperature were set at 75 rpm and 37 ± 0.5°C, respectively. The samples per batch were tested in 900 ml of pH 6.8 phosphate buffer. An aliquot of the release medium was withdrawn at predetermined time intervals and equivalent amount of fresh medium was added to the release medium. The absorption of the samples was recorded at a wavelength of 344 nm spectrophotometrically. Sink conditions were maintained during all measurements.

RESULT AND DISCUSSION

Chloroquine sulphate microspheres were prepared for masking the bitter taste. The reasons to choose solvent evaporation method were its simplicity, low cost and relatively high drug loading. In this study, microspheres prepared with 1:3.9 drug to polymer ratio at 500 rpm were selected for suspension formulations since they have higher loading efficiency and suitable micromeritic properties to disperse in aqueous medium.[13] According to the encapsulation efficiency results obtained in our previous study, the drug content of the microspheres showed good correlation with the theoretical drug loadings.[14] The drug was uniformly encapsulated into the microspheres. The high content of chloroquine sulphate in microspheres was believed to be due to the poor solubility of drug in solvent. The chosen microsphere formulation had 83.89% entrapment efficiency. The threshold value of chloroquine sulphate was found to be 40µg/ml as shown in table 2. SEM image of microspheres as shown in fig.1 that the microspheres were spherical with a smooth surface. The microspheres used had a mean size of 500 µm. As indicated in our previous study that

repose angle value of chosen microsphere formulation was under 30^{O} (25.46^{O}). This result demonstrated that chosen microsphere formulation has suitable flow properties.[15,16]

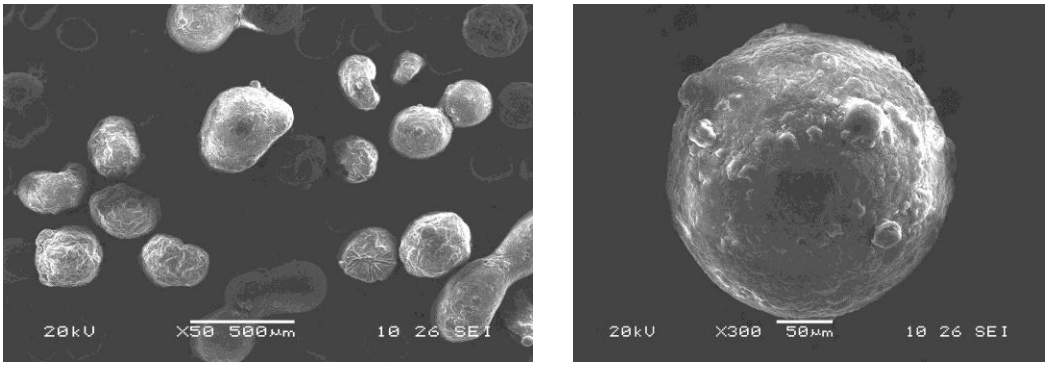

Figure 1: SEM of microsphere

Taste, odour and colour are considered to be important factor for the suspension especially in case of children and elderly patients. All the developed batches of suspension were evaluated for organoleptic properties and all the formulation was found to be most palatable. pH is a considerable factor in case of taste masked suspension. pH acts as barrier and prevent drug to leach out of the polymer. The pH is very important for release of drug from microsphere.[17] The pH of the formulation was found to be from 6.8-6.9.

Viscosity of suspension is very important factor for the stability of suspension because viscosity contributes to rate of sedimentation, higher the viscosity, lower is the rate of sedimentation.[18] The ultimate height of the solid phase after settling depends on the concentration of solid and the particle size. In prepared formulation, there was little sedimentation after 7 and 14 days and it could be easily redispersed and gave uniform dispersion after 2-3 stroke.[19] Results are shown in table 3.

Table 3: Evaluation parameters

Sr.no	Formulation	B1	B2	B3
1	Colour	Orange	Orange	Orange
2	Taste	Sweet	Sweet	Sweet
3	pH	6.8	6.9	6.9
4	Viscosity(cps)	1110	1245	1401
5	Sedimentation volume	0.96	0.95	0.96
6	Redispersibility	85%	85%	85%

The *in-vitro* taste evaluation of suspension in the buffer of salivary pH 6.8 showed that the drug does not get released in saliva to attain threshold bitterness concentrations as shown in table 4 indicates satisfactory taste masking.[20]

Table 4: In vitro threshold value

Formulation	Drug release in Phosphate Buffer pH 6.8	
	30 sec	60 sec
A1	12.54±0.45	17.41±0.34
A2	12.78±0.67	17.78±0.76
A3	12.67±0.75	18.44±1.04

n=3

The drug release profiles of the suspended microspheres and dry microspheres were investigated in pH 6.8 phosphate buffer, as shown in table 5 and Fig. 2. The chloroquine sulphate release rate from the suspended microspheres was consistent with that from dry microspheres.[22] This result indicated that the suspension medium studied did not affect the property of drug release.

Table 5: In vitro drug release

Time(min)	A1 (%)	A2 (%)	A3 (%)
0	0	0	0
5	22.45±0.56	21.88±0.32	19.2±1.03
10	34.56±0.45	32.51±0.78	33.7±0.76
15	45.21±0.76	43.23±0.71	43.22±0.44
20	54.78±1.08	52.41±0.42	51.22±0.89
25	61.44±0.58	59.39±0.74	60.23±0.43
30	65.22±0.55	64.12±0.66	63.23±0.30
35	70.12±0.85	67.43±0.48	66.78±1.09
40	75.32±1.09	74.55±0.73	73.99±0.22
45	79.55±0.56	80.15±0.43	80.12±0.69

n=3

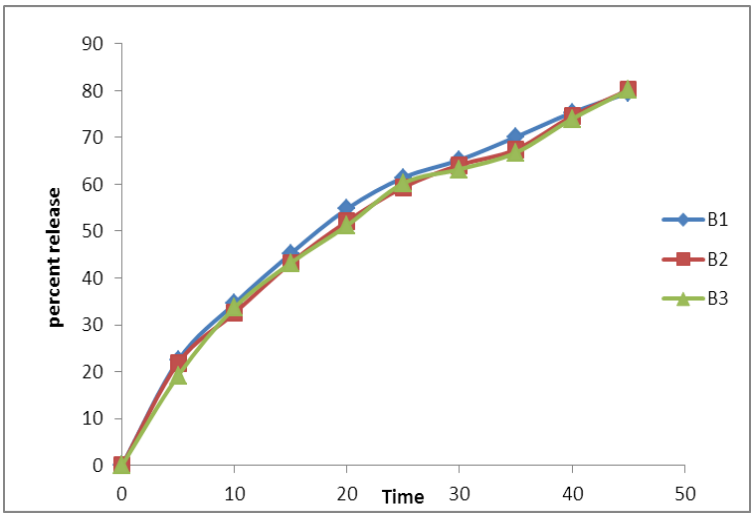

Figure 2: In vitro drug release profile

CONCLUSION

It was concluded that a suspension dosage form of the bitter drug chloroquine sulphate that can enhance compliance in pediatric patients can be prepared by microencapsulation technology. Prepared suspension form was found to have satisfactory in vitro characteristics and stability profile.

ACKNOWLEDGEMENT

The authors are thankful to AISSMS College of Pharmacy, Pune for providing facilities to carry out the research work.

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