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# Formulation and evaluation of the oral dispersible tablets of anti-malarial drugs

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**ABSTRACT**

Optimization of formulation. Physical and In-vitro evaluation of optimized formulation for the release characteristics. Increase the chemical properties like dissolution study. Oral dispersible tablets have received ever-increasing demand during the last decade, and the field has become a rapidly growing area in the pharmaceutical industry. Upon introduction into the mouth, these tablets dissolve or disintegrate in the mouth in the presence of additional water for easy administration of active pharmaceutical ingredients. Optimized formula using polymer coating method exhibited 90% drug release at 15 minutes for model drug but dihydroartemisinin the release was found to be 79% at 15 minutes.



## Introduction

Dispersible tablets are uncoated or film coated tablets intended to be dispersed in water before administration giving a homogeneous dispersion or a stabilized suspension, so, it's preferred in cases where patients cannot swallow a dosage form and the drug substance is unstable if formulated in liquid medication. The faster the drug into solution, the quicker is the absorption and also the onset of action. It is also helpful for patients having prolonged illness who are prone to nauseate sensations if they have to swallow a tablet. The added advantage of this formulation is faster onset of action as compared to standard compressed tablet. The properties of the dispersible tablet, such as porosity, hardness, disintegration time and increase in viscosity after dispersion are necessary to investigate during manufacturing which decides the product performance.

## Materials And Methods

Piperaquietetra phosphate, Dihydroartemisinin Procured from Mylan pharmaceutical, hydrabad, Pregelatinized starch 1500 Magnesium Stearate Procured from Loba chem ,Mumbai ,Microcrystalline cellulose Crosscarmellose sodium Crospovidone Eudragit EPO Procured from signet chemicals, Mumbai.

## Conventional Methodology:

### Piperaquinetetra phosphate

Considering the flow properties was very poor flow of the piperaquine tetraphoaphate, the process of wet granulation was adopted in order to avoid the process problems during manufacturing

### Dihydroartemisinin

Considering the low dosage of the drug that the thermal and moisture issue may occur and as per the literature, it was suggested to be added along with the diluents in the extra granular part.

Various steps included in the formulation

1. Wet granulation of Piperaquine tetraphosphate
2. Dihydroartemisinin was added in extra granular
3. Compression of tablets

**Table 1. Composition of Piperaquinetetraphosphate**

| Ingredients | mg/tab |
|---|---|
| Piperaquine tetraphosphate | 160.00 |
| Pregelatinizedstarch 1500 | 40.00 |
| Dextrin | 8.00 |
| Crosscarmellose sodium | 5.50 |
| HPMC 3 cps | 2.55 |
| **Total weight(mg)** | **216.25** |

### Procedure for preparation of piperaquinetetraphosphate granules

1. All the ingredients were dispensed accurately.
2. Piperaquine tetraphosphate, Pregelatinized starch, Ac-di-sol were sifted through 25 mesh and loaded into Rapid mixer granulator.
3. Dry mixing of the above mixture was done with impeller at 150rpm for 10 mins.
4. Binder solution was prepared by dissolving HPMC 3 cps in purified water
5. Step 3 material was granulated with step 4 binder solution.
6. Granules formed were collected from Rapid mixer granulator and loaded into Rapid dryer and dried for 60 mins at $60^0$C
7. Loss on drying was checked for the granules prepared at $105^0$C for 5mins.
8. Dried granules were milled through quadro-co-mill-fitted with 40G screen at 10hz speed
9. Milled granules were passed through 30mesh.

### Procedure

1. All the ingredients were dispensed accurately.
2. Dihydroartemisinin, diluents, Polyplasdone XL (Crospovidone) wasco-sifted through #30 mesh.
3. Aspartame and cherry flavor were co-sifted through 40 meshand added to step 2and were mixed in polybag properly
4. Piperaquinetetra phosphate granules were added to step 3 and mixed well.
5. Magnesium stearate was sifted through #60 mesh added to the above blend and mixed properly.
6. The blend was then compressed using suitable tooling on rotary compression machine.

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**Inference**

From the above trials, it was found that trial with Avicel PH 102 exhibited lower disintegration time with polyplasdoneXL (crospovidone) when compared with other diluents.

**Procedure**

1. All the ingredients were dispensed properly.
2. Dihydroartemisinin, Avicel PH102, Disintegrantwasco-sifted through #30 mesh and added to bin blender.
3. Required amount of Piperaquine tetraphosphate granules were added to step 2 and blended.
4. Magnesium stearate was sifted through #60 mesh and added to step 3 and blended.
5. The blend was collected in a poly bag and compressed using suitable tooling on rotary compression machine. (9 mm)

**Inference**

From the above formulation trials lower disintegration time was found with .KollidonCL (crospovidone). In compare with other disintegrants Hence Kollidon CL was finalized for the further trials

**Procedure**

1. All the ingredients were dispensed accurately.
2. Piperaquine tetraphosphate,AvicelPH102, Kollidon CL(crospovidone) were co-sifted through #30 mesh and were mixed in polybag properly.
3. Required quantity of Dihydroartemisinin granules were added to step 2 and mixed well.
4. Magnesium stearate was sifted through #60 mesh added to the above blend and mixed properly.
5. The blend was then compressed usingsuitable tooling on rotary compression machine.

**Inference**

From the above trials, it was found that trial without disintegrants shown high disintegration time. There is no significant difference in disintegration time of tablets when disintegrants concentration was raised from 2.5 to 7.5%. Hence disintegrants concentration of 5% was finalized for further trials.

**Procedure**

1. All the ingredients were dispensed accurately.,
2. Dihydroartemisinin,Avicel PH102, and disintegrantswas co-sifted through #30 mesh
3. Piperaquine tetraphosphate granules were added step 2 and mixed well.
4. Magnesium stearate was sifted through #60 mesh added to the above blend and mixed well.
5. The blend was then compressedusing suitable tooling onrotary compression machine

**Inference**

From the above formulation trials it was concluded that trial with kollidon CL exhibited lower disintegration time than the trial with other grades of kollidonCL.Hence Kollidon CL was finalized for the further trials.

**Procedure**

1. All the ingredients were dispensed accurately.
2. Dihydroartemisinin , Avicel PH102, kollidon CL were co-sifted through #30 mesh.
3. Sweetener was sifted through #40 mesh, added to step 2 and mixed well.
4. Piperaquine tetraphosphate granules, were added to step 3 and mixed well.
5. Magnesium stearate was sifted through #60 mesh added to step 4 and mixed well in poly bag.
6. The blend was then compressed using suitable tooling on rotary compression machine**.**

**Inference**

From the above trials it was found that trial with Sucralose and aspartame exhibited acceptable taste when compared to other sweeteners. Hence both the sweeteners were evaluated in further trials.

**Inference**

From the above trials it can be concluded that sucralose is better sweetener than Aspartame.

Trials with sucralose concentration from 20mg-27.5mgwere found to be slightly bitter

Trials with sucralose concentration from 30mg-32.5mg were found to be sweet with no agitation. Hence sucralose concentration of 30mg was selected for further trials.

**Procedure**

1. All the ingredients were dispensed accurately.
2. Dihydroartemisinin , Avicel PH102, kollidon CL were co-sifted through #30 mesh.
3. sucralose and flavors were sifted through #40 mesh,and added to step 2
4. Piperaquine tetraphosphate granules,were added to the step 3 and mixed well in a polybag.
5. Magnesium stearate was sifted through #60 mesh added to step 4blend and mixed well.
6. Step 5 blend was then compressed using suitable tooling on rotary compression machine**.**

**Inference**

From the above trials it can be concluded that, batch with strawberry flavor was found to be pleasant with satisfactory aroma. Hence strawberry flavor of concentration 10mg was finalized.

**Method B**

**Taste Masking By Polymer Coating:**

**Formulation development with Eudragit polymers**

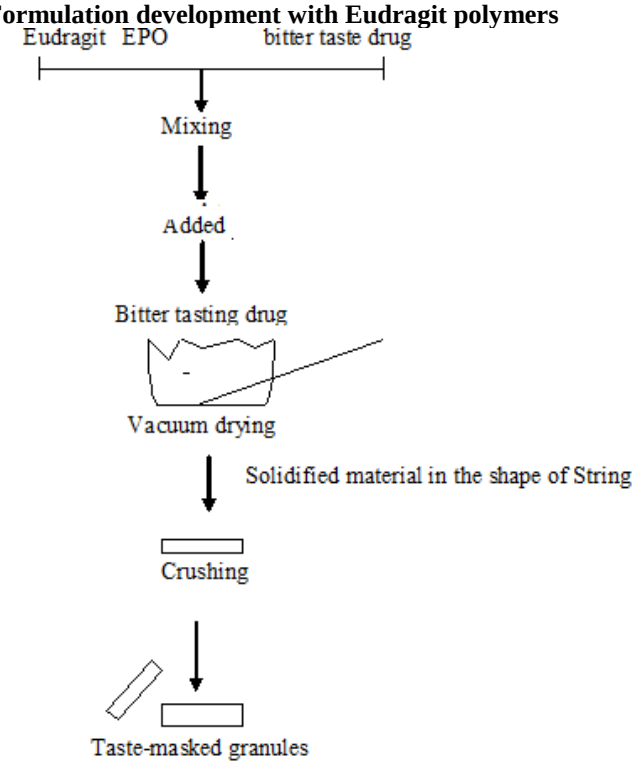



**Fig. Flow chart of formulation of taste masking granules**

**Procedure:**

**Preparation of taste masked granules of Dihydroartemisinin**

Dihydroartemisinin was thoroughly mixed with powdered Eudragit EPO in different ratios. Then 60 % Isopropyl alcohol(IPA)and Dichloromethane 40% was added to this

mixture in a glass beaker and mixed well to make a gelatinous mass. The prepared gel was manually kept in vacuum dryer for drying. After extrusion, IPA and DCM was removed by evaporation overnight at room temperature. Subsequently the solidified drug polymer complex (DPC) was crushed into granules using a mortar.

Three batches were prepared containing drug- Eudragit EPO in the ratio of 1:1, 1:2 , and 1:3 in IPA and DCM by the above-mentioned method.

**Inference**

From the above trials it was found that the drug polymer ratio of 1:3 was able to mask the bitterness of the drug completely. Hencedrug polymer ratio of 1:3 was further optimized.

**Procedure**

1. All the ingredients were dispensed properly.,
2. AvicelPH102 and Disintegrants were co-sifted through #30 mesh and mixed well.
3. Piperaquine tetraphosphategranules and Mode 2 drug granules were added to step 2
4. Magnesium stearate was sifted through #60 mesh and added to step 3 and mixed well.
5. Step 4 blend was compressed using suitable tooling on rotary compression machine using suitable tooling(9 mm)

**Inference**

From the above trials, it was found that the trial with different disintegrants shown with same concentration there is significant change in disintegration time in compare with other disintegrant .the lower disintegration time was found with kollidonCL (crospovidone).Hence Kollidon CL was optimized for further trials

**Procedure**

1. All the ingredients were dispensed accurately.
2. Avicel PH102 and kollidon CL were co-sifted through #30 mesh
3. Sweetener was sifted through #40 mesh, and added to step 2 and mixed well.
4. Piperaquine tetraphosphate granules and Dihydroartemisinin granules were added to step 3 and mixed well.
5. Magnesium stearate was sifted through #60 mesh added to step 4 and mixed well.
6. Step 5 blend was then compressed using suitable tooling on rotary compression machine using suitable tooling**.**

**Inference**

From the above trials it was found that trial with Sucralose and aspartame exhibited acceptable taste when compared to other sweeteners. Hence both the sweeteners were evaluated in further trials

**Inference**

From the above trials it can be concluded that sucralose is better sweetener than asparatame.

Trials with sucralose concentration from 5mg-12.5mgwere found to be slightly bitter

Trials with sucralose concentration from 15mg17.5mg were found to be sweet with no agitation .Hence sucralose concentration of 30mg was selected for further trials.

**Procedure**

1. All the ingredients were dispensed accurately.
2. Avicel PH102 and kollidon CL were co-sifted through #30 mesh .
3. Sweetener Sucralose was sifted through #40 mesh, added to step 2.
4. Piperaquine tetraphosphate granules and Dihydroartemisinin granules were added to step 3 and mixed well.
5. Magnesium stearate was sifted through #60 mesh added to step 4 and mixed well.
6. Step blend was then compressedusing suitable toolingonrotary compression machine

**Inference**

From the above trials it can be concluded that, batch with strawberry flavor was found to be pleasant with satisfactory aroma. Hence strawberry flavor of concentration 10mg was finalized.

**Inference**

**1.** All the physical parameters were found to be satisfactory
**2.** Sweetener sucralose found to be sweet with no agitation
**3.** Strawberry flavor was found to be pleasant and satisfactory aroma

Hence conventional method was successfully achieved

**Inference**

**1.** All the physical parameter of the formulation were found to be satisfactory
**2.** Dihydroartemisinin was coated with polymer Eudragit EPO was able to mask the bitter ness completely and found to be satisfactory
**3.** Sweetenersucralose found to be sweet with no agitation
**4.** strawberry flavor was found to be pleasant and satisfactory aroma

Hence taste masking by polymer coating method was successfully achieved.

**Results And Discussion**

**Physical characterization drugs 1 and 2**

**Inference**

From above studies, it was concluded that both the drugs are having very very poor flow properties.

**Inference**

From the above studies, it was concluded that blend of optimized formulation A and B **e**xhibited passable flow properties

**Sieve analysis**

**For Piperaquine tetraphosohate**

**Inference**

From the above study it was observed that around 97% of sample retained on 40# mesh which concluded that the average particle size of piperaquine tetra phosohate is more than 420 microns

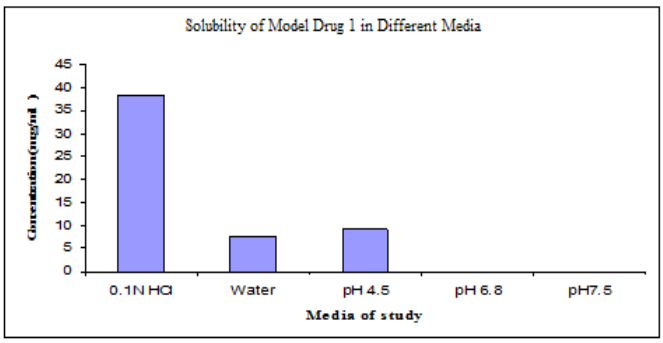



**Fig 1. Solubility profile of piperaquine tetra phosohate in different media**

**For Dihydroartemisinin**

**Inference**

From the above study it was observed that cumulative retained on 60 mesh was around 89%

**Inference**

From the above study it was observe that the cumulative percentage of sample retained
On 60 mesh was 28% whereas fines through 100 mesh was 24%

**Solubility studies**

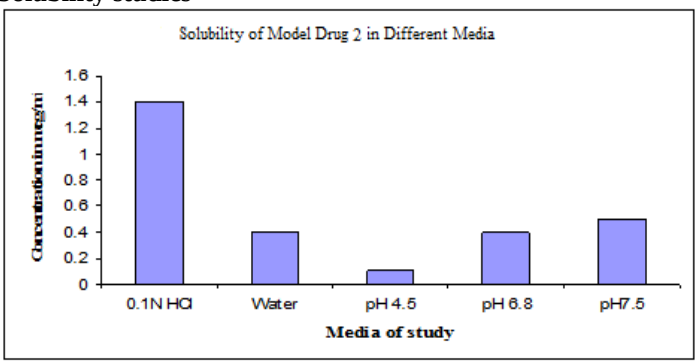



**Fig 2. Solubility profile of dihydroartemisinin in different media**

**Inference**

From the above solubility it can be concluded that the piperaquine tetra phosohateand dihydroartemisinin are having highest solubility in 0.1 N HCL. Compared with other medium.

**Method development**

**Determination of $\lambda_{max}$**

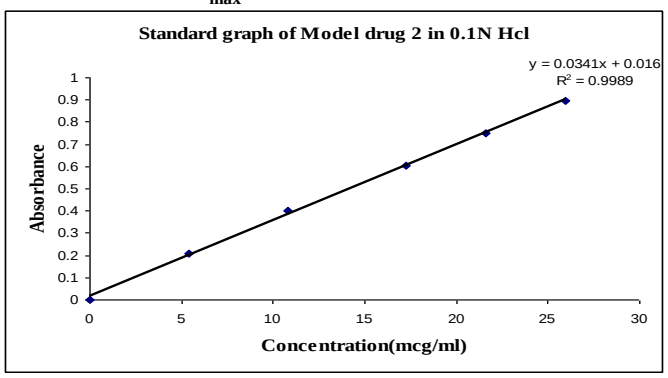



**Fig12.1: Standard graph of Piperquinetetraphosphate in 0.1N HCl**

**Inference:**

The $\lambda_{max}$ of model drug was found to be 345nm**.** The linear equation was y = 0.0339x + 0.0216 (x=concentration µg/ml). Different standard concentration and their absorbance values were shown in the table . Regression value of the calibration curve is 0.9979.

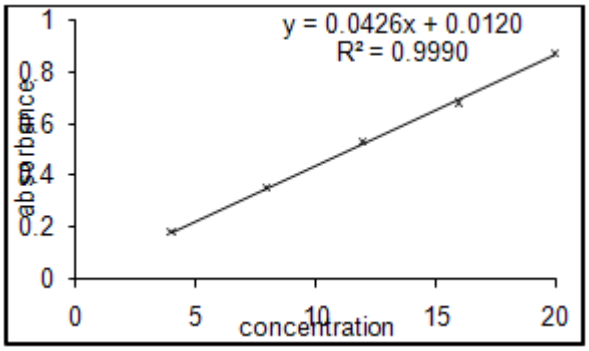



**Figure 4. Standard graph of dihydroartemisinin in 0.1N HCL.**

**Inference:**

The $\lambda_{max}$ of model drug was found to be 210nm**.** The linear equation was y = 0.0426x + 0.0120 (x=concentration µg/ml). Different standard concentration and their absorbance values were shown in the table. Regression value of the calibration curve is 0.9990.

**Drug Interaction studies:**

**Thermogram Of Piperquinetetraphosphate**

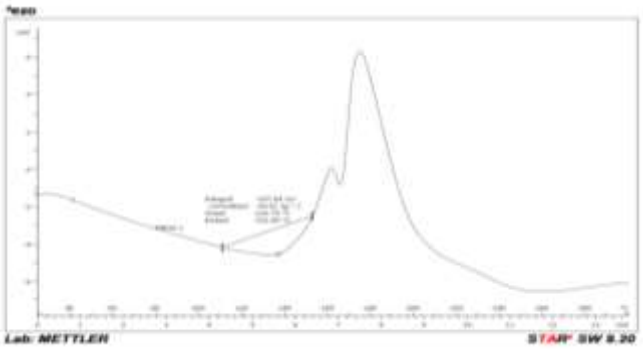



**Figure 4. DSC thermo gram of the Model drug**

**DSC Thermogram of Dihydroartemisinin**

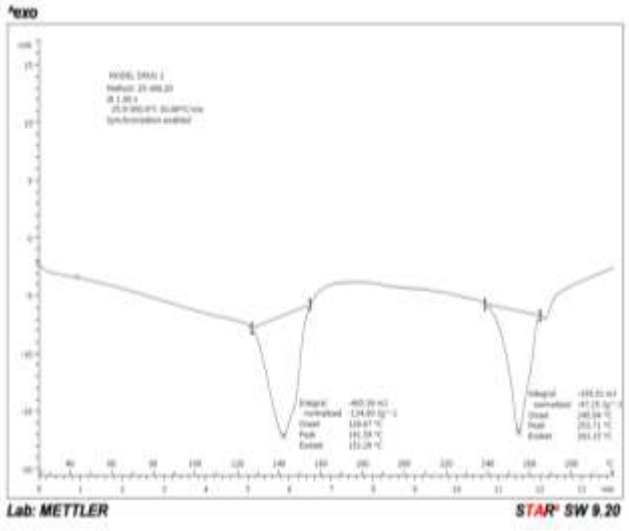



**Figure 5. DSC thermo gram of the Dihydroartemisinin**

**Inference**

From the above thermo grams, it was found that the melting point of Piperaquine tetra phosohate was $154^0$C and that of Dihydroartemisinin was $253^0$C.

**DSC Thermogram Of Piperquinetetraphosphate, Iimixture**

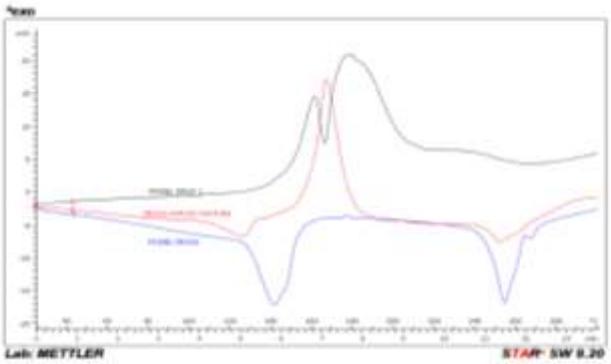



**Figure 6. DSC of drug mixture with individual drugs**

**DSC thermograms of AC-DI-SOL**

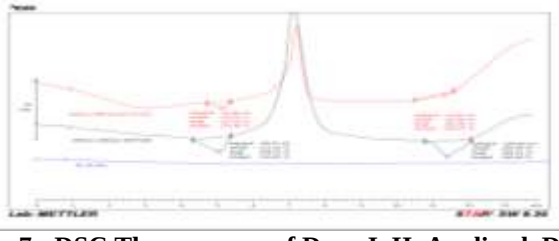


**Figure 7 : DSC Thermogram of Drug I, II, Ac-di-sol, Drug I, II and Ac-di-so**

**Table 2. Composition of Trails with Different Diluents**

| Ingredients | F1 | F2 | F3 | F4 | F5 |
|---|---|---|---|---|---|
| Piperaquine tetraphosphate Granules | 216.25 | 216.25 | 216.25 | 216.25 | 216.25 |
| Extra Granular Portion | | | | | |
| Dihydroartemisinin | 20.00 | 20.00 | 20.00 | 20.00 | 20.00 |
| Microcrystalline cellulose (Avicel PH102) | 38.55 | - | - | - | - |
| Microcrystalline cellulose (Avicel PH101) | - | 38.55 | - | - | - |
| Mannitol SD100 (pearlitol) | - | - | 38.55 | - | - |
| Mannitol SD200 (pearlitol) | - | - | - | 38.55 | - |
| Pre-gelatinised starch | - | - | - | - | 38.55 |
| PolyplasdoneXL(crospovidone) | 15.00 | 15.00 | 15.00 | 15.00 | 15.00 |
| Aspartame | 5.00 | 5.00 | 5.00 | 5.00 | 5.00 |
| Cherry flavor | 2.00 | 2.00 | 2.00 | 2.00 | 2.00 |
| Magnesium stearate | 3.00 | 3.00 | 3.00 | 3.00 | 3.00 |
| Total weight (mg) | 300 | 300 | 300 | 300 | 300 |

**Table 3 Physical parameters of Trails on Different Diluents**

| Parameters | F1 | F2 | F3 | F4 | F5 |
|---|---|---|---|---|---|
| Thickness(mm) | 3.53-3.62 | 3.55-3.65 | 3.52-3.61 | 3.55-3.62 | 3.51-3.60 |
| Hardness(kp) | 4.3-5.4 | 4.5-6.0 | 4.1-5.8 | 4.6-5.4 | 4.8-5.8 |
| Disintegration time(mins′ sec″) | 1′ 5″-1′20″ | 1′20″-1′55″ | 1′30″-2′10″ | 1′30″-2′5″ | 2′5″-2′18″ |

**Table 4 Composition of Trail with different Disintegrants**

| Composition | F1 | F2 | F3 | F4 | F5 |
|---|---|---|---|---|---|
| Piperaquine tetraphosphate Granules | 216.25 | 216.25 | 216.25 | 216.25 | 216.25 |
| EG Portion | | | | | |
| Dihydroartemisinin | 20 | 20 | 20 | 20 | 20 |
| Microcrystalline cellulose(AvicelPH102) | 38.55 | 38.55 | 38.55 | 38.55 | 38.55 |
| Low Substituted Hydroxypropyl Cellulose (LHPCLH11) | 15.00 | - | - | - | - |
| Crospovidone (Kollidon CLM) | - | 15.00 | | - | - |
| Low Substitute Hydroxyl Propyl Cellulose (LHPC LH21) | - | - | 15.00 | | - |
| Low Substituted Hydroxypropyl Cellulose (LHPC LH31) | - | - | - | 15.00 | |
| Crosscarmellose Sodium | - | - | - | - | 15.00 |
| Aspartame | 5.00 | 5.00 | 5.00 | 5.00 | 5.00 |
| Cherry flavor | 2.00 | 2.00 | 2.00 | 2.00 | 2.00 |
| Magnesium stearate | 3.00 | 3.00 | 3.00 | 3.00 | 3.00 |
| Total weight(mg) | 300 | 300 | 300 | 300 | 300 |

**Table 5. Composition of Trail with different Disintegrants F6-F9**

| Ingredients | F6 | F7 | F8 | F9 |
|---|---|---|---|---|
| Piperaquine tetraphosphate Granules | 216.25 | 216.25 | 216.25 | 216.25 |
| Extra granular Portion | | | | |
| Dihydroartemisinin | 20 | 20 | 20 | 20 |
| Microcrystalline cellulose(AvicelPH102) | 38.55 | 38.55 | 38.55 | 38.55 |
| PolyplasdoneXL(crospovidone) | 15.00 | - | - | - |
| PolyplasdoneXL 10(crospovidone) | - | 15.00 | | - |
| Kollidon CL (crospovidone) | - | - | 15.00 | |
| Sodium starch glycolate | - | - | - | 15.00 |
| Aspartame | 5.00 | 5.00 | 5.00 | 5.00 |
| Cherry flavor | 2.00 | 2.00 | 2.00 | 2.00 |
| Magnesium stearate | 3.00 | 3.00 | 3.00 | 3.00 |
| Total weight(mg) | 300 | 300 | 300 | 300 |

**Table 6. Physical parameters of Trails on Different Disintegrants F1-F9**

| Formulations | Thickness(mm) | Hardness(kp) | D.T(mins′ sec″) |
|---|---|---|---|
| F1 | 3.53-3.62 | 4.5-5.7 | 1′ 5″-1′20″ |
| F2 | 3.55-3.65 | 4.5-5.6 | 1′ 4″-1′40″ |
| F3 | 3.51-3.59 | 4.2-5.5 | 1′ 20″-2′10″ |
| F4 | 3.53-3.62 | 4.4-5.6 | 1′3 5″-2′45″ |
| F5 | 3.52-3.63 | 4.2-5.7 | 1′ 5″-1′20″ |
| F6 | 3.55-3.69 | 4.3-5.8 | 1′ 5″-1′50″ |
| F7 | 3.53-3.64 | 4.2-5.9 | 1′ 20″-1′53″ |
| F8 | 3.55-3.64 | 4.3-5.7 | 1′-1′20″ |
| F9 | 3.51-3.62 | 4.4-5.6 | 1′-1′20″ |

**Table 7. Formulation with different concentrations of Kollidon-CL**

| Ingredients | without | 2.5% | 5% | 7.5% |
|---|---|---|---|---|
| Piperaquine tetraphosphate Granules | 216.25 | 216.25 | 216.25 | 216.25 |
| Extra Granular Portion | | | | |
| Dihydroartemisinin | 20 | 20 | 20 | 20 |
| Microcrystalinecellulose (AvicelPH102) | 53.55 | 46.25 | 38.55 | 31.25 |
| Kollidon CL (crospovidone) | - | 5.5 | 15 | 22.5 |
| Aspartame | 5.00 | 5.00 | 5.00 | 5.00 |
| Cherry flavor | 2.00 | 2.00 | 2.00 | 2.00 |
| Magnesium stearate | 3.00 | 3.00 | 3.00 | 3.00 |
| Total weight (mg) | 300 | 300 | 300 | 300 |

**Table 8. Evaluation parameters**

| Parameters | Kollidon CL 0% | Kollidon CL 2.5% | Kollidon CL 5% | Kollidon CL 7.5% |
|---|---|---|---|---|
| Thickness(mm) | 3.55-3.61 | 3.53-3.63 | 3.52-3.60 | 3.55-3.61 |
| Hardness(kp) | 4.4-5.6 | 4.2-5.8 | 4.4-5.5 | 4.1-5.8 |
| Disintegration Time (min′ -sec″) | 2′ 30″-3′10″ | 1′ 50″-2′30″ | 1′ 00″- 1′10″ | 55″-1′ 05 ″ |

**Table 9. Formulation with different grades of Kollidon(crospovidone)**

| Ingredients | F1 | F2 | F3 | F4 |
|---|---|---|---|---|
| Piperaquine tetraphosphate Granules | 216.25 | 216.25 | 216.25 | 216.25 |
| Extra Granular Portion | | | | |
| Model drug 2 | 38.55 | 38.55 | 38.55 | 38.55 |
| Microcrystalline cellulose (AvicelPH102) | 38.55 | 38.55 | 38.55 | 38.55 |
| Kollidon CL (crospovidone) | 15.00 | - | - | - |
| Kollidon CL-F (crospovidone) | - | 15.00 | - | - |
| Kollidon 90F (crospovidone) | - | - | 15.00 | - |
| Kollidon CL- M (crospovidone) | - | - | - | 15.00 |
| Aspartame | 5.00 | 5.00 | 5.00 | 5.00 |
| Cherry flavor | 2.00 | 2.00 | 2.00 | 2.00 |
| Magnesium stearate | 3.00 | 3.00 | 3.00 | 3.00 |
| Total weight (mg) | 300 | 300 | 300 | 300 |

**Table 10. Evaluation parameters**

| Parameters | Hardness(kp) | Thickness(mm) | Disintegrationtime (min′ -sec″) |
|---|---|---|---|
| Kollidon CL | 4.5-5.7 | 3.55-3.61 | 58″-1′ 05″ |
| Kollidon CL-F | 4.3-5.6 | 3.53-3.62 | 1′ -1′ 50″ |
| Kollidon CL-SF | 4.1-5.7 | 3.52-3.60 | 1′-1′53″ |
| Kollidon CL-M | 4.2-5.8 | 3.55-3.59 | 1′5″ -1′65″ |

**Table 11**

| Ingredients | Sucralose | Aspartame | Acesulfame potassium | Sodium Saccharin | Sucrose | Pulverized sugar |
|---|---|---|---|---|---|---|
| Piperaquine tetraphosphate Granules | 216.25 | 216.25 | 216.25 | 216.25 | 216.25 | 216.25 |
| Extra Granular Portion | | | | | | |
| Model drug2 | 20 | 20 | 20 | 20 | 20 | 20 |
| Microcrysta-line cellulose (AvicelPH102) | 38.55 | 38.55 | 38.55 | 38.55 | 38.55 | 38.55 |
| Kollidon CL crospovidone | 15.00 | 15.00 | 15.00 | 15.00 | 15.00 | 15.00 |
| Sucralose | 25.00 | - | - | - | - | - |
| Aspartame | - | 25.00 | - | - | - | - |
| Acesulfame Potassium | - | - | 25.00 | - | - | - |
| Sodium Saccharin | - | - | - | 25.00 | - | - |
| Sucrose | - | - | - | - | 25.00 | - |
| Pulverized sugar | - | - | - | - | - | 25.00 |
| Cherry flavor | 2.00 | 2.00 | 2.00 | 2.00 | 2.00 | 2.00 |
| Magnesium stearate | 3.00 | 3.00 | 3.00 | 3.00 | 3.00 | 3.00 |
| Total weight (mg) | 320 | 320 | 320 | 320 | 320 | 320 |

**Table 12. Formulation with different levels of aspartame**

| Ingredients | Trial 1 | Trial 2 | Trial 3 | Trial 4 | Trial 5 | Trial 6 |
|---|---|---|---|---|---|---|
| Piperaquine tetraphosphate Granules | 216.25 | 216.25 | 216.25 | 216.25 | 216.25 | 216.25 |
| Extra Granular Portion | | | | | | |
| Dihydroartemisinin | 20.00 | 20.00 | 20.00 | 20.00 | 20.00 | 20.00 |
| Microcrystalinecellulose (Avicel PH102) | 43.55 | 41.25 | 38.55 | 36.25 | 33.55 | 31.25 |
| kollidon CL(crospovidone) | 15.00 | 15.00 | 15.00 | 15.00 | 15.00 | 15.00 |
| Aspartame | 20.00 | 22.5 | 25.00 | 27.5 | 30.00 | 32.5 |
| Cherry flavor | 2.00 | 2.00 | 2.00 | 2.00 | 2.00 | 2.00 |
| Magnesium stearate | 3.00 | 3.00 | 3.00 | 3.00 | 3.00 | 3.00 |
| Total weight (mg) | 320 | 320 | 320 | 320 | 320 | 320 |

**Table 13 Formulation with different levels of Sucralose**

| Ingredients | Trial 1 | Trial 2 | Trial 3 | Trial 4 | Trial 5 | Trial 6 |
|---|---|---|---|---|---|---|
| Piperaquine tetraphosphate Granules | 216.25 | 216.25 | 216.25 | 216.25 | 216.25 | 216.25 |
| Exta Granular Portion | | | | | | |
| Dihydroartemisinin | 20.00 | 20.00 | 20.00 | 20.00 | 20.00 | 20.00 |
| Microcrystalinecellulose (Avicel PH102) | 43.55 | 41.25 | 38.55 | 36.25 | 33.55 | 31.25 |
| Kollidon CL (cropovidone) | 15.00 | 15.00 | 15.00 | 15.00 | 15.00 | 15.00 |
| Sucralose | 20 | 22.5 | 25 | 27.5 | 30 | 32.5 |
| Cherry flavor | 2.00 | 2.00 | 2.00 | 2.00 | 2.00 | 2.00 |
| Magnesium stearate | 3.00 | 3.00 | 3.00 | 3.00 | 3.00 | 3.00 |
| Total weight (mg) | 320 | 320 | 320 | 320 | 320 | 320 |

**Table 14. Formulation of with Sucralose and different levels of flavors**

| Ingredients | F1 | F2 | F3 | F4 | F5 |
|---|---|---|---|---|---|
| Piperaquine tetraphosphate Granules | 216.25 | 216.25 | 216.25 | 216.25 | 216.25 |
| Extra Granular Portion | | | | | |
| Microcrystalinecellulose (AvicelPH102) | 33.55 | 33.55 | 33.55 | 33.55 | 33.55 |
| Dihydroartemisinin | 20.00 | 20.00 | 20.00 | 20.00 | 20.00 |
| KollidonCL (crospovidone) | 15.00 | 15.00 | 15.00 | 15.00 | 15.00 |
| Sucralose | 30 | 30 | 30 | 30 | 30 |
| Orange juice flavor | 10.00 | - | - | - | - |
| Orange flavor | - | 10.00 | - | - | - |
| Pepper-mint flavor | - | - | 10.00 | - | - |
| Cherry flavor | - | - | - | 10.00 | - |
| Strawberry flavor | - | - | - | - | 10.00 |
| Magnesium stearate | 3 | 3 | 3 | 3 | 3 |
| Total weight (mg) | 330 | 330 | 330 | 330 | 300 |

**Table-15**

| Ingredients | mg/tab | Ratio 1:1 | Ratio 1:2 | Ratio 1:3 |
|---|---|---|---|---|
| Piperaquine tetraphosphate | 20 | 20 | 20 | 40 |
| Eudragit EPO | 80 | 80 | 160 | 60 |
| IPA | 40 | 40 | 40 | 40 |
| DCM | 60 | 60 | 60 | 60 |

**Table 16 Formulation with different Disintegrants**

| Ingredients | F1 | F2 | F3 |
|---|---|---|---|
| Dihydroartemisinin granules | 216.20 | 216.25 | 216.25 |
| Piperaquine tetraphosphate granules | 20 | 20 | 20 |
| Extra granular | | | |
| Microcrystalinecellulose(AvicelPH102) | 38.55 | 38.55 | 38.55 |
| PolyPlasadoneXL(crospovidone) | 15.00 | - | - |
| Kollidon CL(crospovidone) | - | 15.00 | - |
| Sodium starch glycolate | - | - | 15.00 |
| Aspartame | 5.00 | 5.00 | 5.00 |
| Cherry flavor | 2.00 | 2.00 | 2.00 |
| Magnesium stearate | 3.00 | 3.00 | 3.00 |
| Total weight(mg) | 300 | 300 | 300 |

| Parameters | Hardness(kp) | Thickness(mm) | Disintegration time (min′ -sec″) |
|---|---|---|---|
| FI | 4.5-5.7 | 3.55-3.61 | 55″-1′ 05″ |
| F2 | 4.3-5.6 | 3.53-3.62 | 1′05″ -1′35″ |
| F3 | 4.1-5.7 | 3.52-3.60 | 1′-1′40″ |

**Table 17 Composition of different trials with Sweeteners**

| Ingredients | Sucralose | Aspartame | Acesulfame potassium | Sodium Saccharin | Sucrose | Pulverized sugar |
|---|---|---|---|---|---|---|
| Piperaquine tetraphosphate Granules | 216.25 | 216.25 | 216.25 | 216.25 | 216.25 | 216.25 |
| Dihydroartemisinin Granules | 20 | 20 | 20 | 20 | 20 | 20 |
| Extra Granular Portion | | | | | | |
| Microcrysta-line cellulose (AvicelPH102) | 38.55 | 38.55 | 38.55 | 38.55 | 38.55 | 38.55 |
| Kollidon CL crospovidone | 15.00 | 15.00 | 15.00 | 15.00 | 15.00 | 15.00 |
| Sucralose | 15.00 | - | - | - | - | - |
| Aspartame | - | 15.00 | - | - | - | - |
| Acesulfame Potassium | - | - | 15.00 | - | - | - |
| Sodium Saccharin | - | - | - | 15.00 | - | - |
| Sucrose | - | - | - | - | 15.00 | - |
| Pulverized sugar | - | - | - | - | - | 15.00 |
| Strawberry flavor | 2.00 | 2.00 | 2.00 | 2.00 | 2.00 | 2.00 |
| Magnesium stearate | 3.00 | 3.00 | 3.00 | 3.00 | 3.00 | 3.00 |
| Total weight (mg) | 300 | 300 | 300 | 300 | 300 | 300 |

**Table 18 Composition of Trial with different levels of Aspartame**

| Ingredients | Trial 1 | Trial 2 | Trial 3 | Trial 4 | Trial 5 | Trial 6 |
|---|---|---|---|---|---|---|
| Piperaquine tetraphosphate Granules | 216.25 | 216.25 | 216.25 | 216.25 | 216.25 | 216.25 |
| Dihydroartemisinin | 20 | 20 | 20 | 20 | 20 | 20 |
| Extragranular | | | | | | |
| Microcrystaline cellulose (Avicel PH102) | 43.55 | 41.25 | 38.55 | 36.25 | 33.55 | 31.25 |
| KollidonCL (crospovidone) | 15.00 | 15.00 | 15.00 | 15.00 | 15.00 | 15.00 |
| Aspartame | 5.00 | 7.50 | 10.00 | 12.50 | 15.00 | 17.50 |
| Cherry flavor | 2.00 | 2.00 | 2.00 | 2.00 | 2.00 | 2.00 |
| Magnesium stearate | 3.00 | 3.00 | 3.00 | 3.00 | 3.00 | 3.00 |
| Total weight (mg) | 310 | 310 | 310 | 310 | 310 | 310 |

**Table 19. Composition of Trial with different levels of Sucralose**

| Ingredients | Trial 1 | Trial 2 | Trial 3 | Trial 4 | Trial 5 | Trial 6 |
|---|---|---|---|---|---|---|
| Piperaquine tetraphosphate Granules | 216.25 | 216.25 | 216.25 | 216.25 | 216.25 | 216.25 |
| Dihydroartemisinin | 20 | 20 | 20 | 20 | 20 | 20 |
| Extragranular | | | | | | |
| Microcrystaline cellulose (Avicel PH102) | 43.55 | 41.25 | 38.55 | 36.25 | 33.55 | 31.25 |
| KollidonCL (crospovidone) | 15.00 | 15.00 | 15.00 | 15.00 | 15.00 | 15.00 |
| Sucralose | 5.00 | 7.50 | 10.00 | 12.50 | 15.00 | 17.50 |
| Cherry flavor | 2.00 | 2.00 | 2.00 | 2.00 | 2.00 | 2.00 |
| Magnesium stearate | 3.00 | 3.00 | 3.00 | 3.00 | 3.00 | 3.00 |
| Total weight (mg) | 320 | 320 | 320 | 320 | 320 | 320 |

**Table 20. Composition of Trials with different flavors with Sucralose**

| Ingredients | Orange juice | Orange | Pepper- mint | Cherry | Strawberry |
|---|---|---|---|---|---|
| Piperaquine tetraphosphate Granules | 216.25 | 216.25 | 216.25 | 216.25 | 216.25 |
| Dihydroartemisinin granules | 20 | 20 | 20 | 20 | 20 |
| Extragranular | | | | | |
| Microcrystalinecellulose (Avicel PH102) | 33.55 | 33.55 | 33.55 | 33.55 | 33.55 |
| Kollidon CL (crospovidone) | 15.00 | 15.00 | 15.00 | 15.00 | 15.00 |
| Sucralose | 30.00 | 30.00 | 30.00 | 30.00 | 30.00 |
| Orange juice flavor | 10.00 | - | - | - | - |
| Orange flavor | - | 10.00 | - | - | - |
| Pepper- mint flavor | - | - | 10.00 | - | - |
| Cherry flavor | - | - | - | 10. .00 | - |
| Strawberry flavor | - | - | - | - | 10.00 |
| Magnesium stearate | 3.00 | 3.00 | 3.00 | 3.00 | 3.00 |
| Total weight (mg) | 330 | 330 | 330 | 330 | 300 |

**Table 21. Optimized formula using conventional taste masking methodology**

| Ingredients | Optimized Trail 1 |
|---|---|
| Dihydroartemisinin granules | 216.25 |
| EG Portion | |
| Dihydroartemisinin | 20.00 |
| Microcrystalinecellulose(Avicel PH102) | 25.75 |
| Kollidon CL(crospovidone) | 15.00 |
| Sucralose | 30.00 |
| strawberry flavor | 10.00 |
| Magnesium stearate | 3.00 |
| Total weight(mg) | 320 |

**Table 22 Evaluation parameters**

| Parameters | Hardness (kp) | Thickness(mm) | Disintegration time (min' – sec") |
|---|---|---|---|
| Optimized batch | 4.5-5.8 | 3.58-3.64 | 0′.58″-1′ 05″ |

**Table 23. Optimized formula using taste masking by polymer coating**

| Ingredients | Optimized Trail |
|---|---|
| Dihydroartemisinin granules | 216.25 |
| Piperaquine tetraphosphate granules | 20.00 |
| Extragranular | |
| Microcrystalinecellulose(Avicel PH102) | 30.75 |
| Kollidon CL(crospovidone) | 15 |
| Sucralose | 15 |
| strawberry flavor | 10 |
| Magnesium stearate | 3 |
| Total weight(mg) | 310 |

**Table 24. Evaluation parameter**

| Parameters | Hardness(kp) | Thickness (mm) | Disintegration time(min' – sec") |
|---|---|---|---|
| Optimized batch | 4.5-5.6 | 3.58-3.64 | 0′.50″-1′0″ |

**Table 25 Flow properties of both the Model drugs**

| Parameter | Piperaquine tetra phosohate | Dihydroartemisinin |
|---|---|---|
| Tapped density(gm/ml) | 0.733 | 0.333 |
| Bulk density( gm/ml) | 0.407 | 0.155 |
| Carr's Compressibility index(%) | 44.44 | 53.45 |
| Hausner's Ratio | 1.80 | 2.14 |

**Table 26 Flow properties of lubricated blend of the Conventional Methodology**

| Parameter | Blend |
|---|---|
| Tapped density(gm/ml) | 0.5235 |
| Bulk density( gm/ml) | 0.364 |
| Carr's Compressibility index(%) | 25.098 |
| Hausner's Ratio | 1.644 |

**Table 27 Flow properties of lubricated blend of taste masking of the polymer coating**

| Parameter | Blend |
|---|---|
| Tapped density(gm/ml) | 0.5029 |
| Bulk density( gm/ml) | 0.379 |
| Carr's Compressibility index(%) | 25.902 |
| Hausner's Ratio | 1.326 |

**Table 28. Particle size determination of piperaquine tetraphosohate**

| Sieve Mesh Number | Sieve Size Opening(μm) | Mass of Sample Retained on each Sieve (g) | Percentage of Sample Retained on each Sieve (%) | Cumulative Percentage of Sample Retained on Each Sieve (%) |
|---|---|---|---|---|
| 40 | 420 | 9.92 | 96.498 | 96.498 |
| 60 | 250 | 0.1 | 0.972 | 97.47 |
| 80 | 177 | 0.14 | 1.361 | 98.831 |
| 100 | 149 | 0.06 | 0.583 | 99.414 |
| Pan | - | 0.06 | 0.583 | 99.997 |

**Table 29 Particle size determination of dihydroartemisinin**

| Sieve Mesh Number | Sieve Size Opening(µm) | Mass of Sample Retained on Each Sieve(g) | Percentage of Sample Retained on Each Sieve (%) | Cumulative Percentage of Sample Retained on Each Sieve (%) |
|---|---|---|---|---|
| 40 | 420 | 10.78 | 52.94 | 52.94 |
| 60 | 250 | 7.34 | +36.051 | 88.991 |
| 80 | 177 | 1.28 | 6.286 | 95.277 |
| 100 | 149 | 0.61 | 2.996 | 98.273 |
| Pan | - | 0.35 | 1.719 | 99.992 |

**Table 30 Particle size determination of blend**

| Sieve Mesh Number | Sieve Size Opening(µm) | Mass of Sample Retained on Each Sieve(g) | Percentage of Sample Retained on Each Sieve (%) | Cumulative Percentage of Sample Retained on Each Sieve (%) |
|---|---|---|---|---|
| 40 | 420 | 1.4 | 6.89 | 6.89 |
| 60 | 250 | 4.32 | 21.29 | 28.18 |
| 80 | 177 | 5.08 | 25.036 | 53.216 |
| 100 | 149 | 4.63 | 22.819 | 76.035 |
| Pan | - | 4.86 | 23.952 | 99.987 |

**Table 31. Solubility study of both the drugs 1 & 2**

| Media | Solubility ( mg/ml) | |
|---|---|---|
| | Piperaquine tetra phosohate | Dihydroartemisinin |
| 0.1N HCl | 38.3 | 1.4 |
| Water | 7.6 | 0.4 |
| pH 4.5 | 9.22 | 0.1 |
| pH 6.8 | 0.05 | 0.4 |
| pH7.5 | 0.03 | 0.5 |

**Table 32 Determination of $\lambda_{max}$ for Piperaquine tetra phosohate**

| Concentration (mcg/ml) | Absorbance |
|---|---|
| 0 | 0 |
| 5.4 | 0.21 |
| 10.8 | 0.4 |
| 17.28 | 0.603 |
| 21.6 | 0.748 |
| 25.92 | 0.895 |

**Table 33 Determination of $\lambda_{max}$ for Dihydroartemisinin**

| Concentration (ug/ml) | Absorbance |
|---|---|
| 4 | 0.182 |
| 8 | 0.353 |
| 12 | 0.529 |
| 16 | 0.679 |
| 20 | 0.870 |

**Table 34. Physical observation of drug and excipient blends**

| Blend | Description | | |
|---|---|---|---|
| | Initial | 40˚C 75%RH 15 days | 30˚C 75%RH 15 weeks |
| drugs + Micro crystalline cellulose | White powder | White powder | White powder |
| drugs + Ac-di-sol | White to grayish white powder | White to grayish white powder | White to grayish white powder |
| drugs + kollidon CL | White to creamy white powder | White to creamy white powder | White to creamy white powder |
| drugs + EPO | White powder | White powder | White powder |
| drugs + sucrolose | White powder | White powder | White powder |
| drugs + HPMC3CPS | White to creamy white powder | White to creamy white powder | White to creamy white powder |
| drugs + Magnesium stearate | Light white powder | Light white powder | Light white powder |

**Table 36. Dissolution Profile of Piperquinetetraphosphate (Final formulation)**

| Time(mins) | % Drug release |
|---|---|
| 5 | 77 |
| 10 | 85 |
| 15 | 89 |
| 30 | 92 |
| 45 | 95 |
| 60 | 97 |

**DSC Thermograms of HPMC**

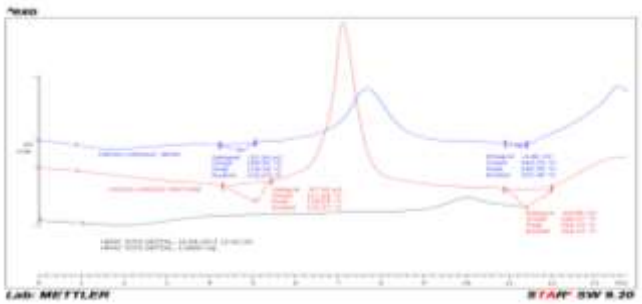


**Figure 8. DSC Thermogram of Drug I, II, HPMC, Drug I, II and HPMC**

**DSC thermograms of micro crystalline Cellulose PH 102 (MCC)**

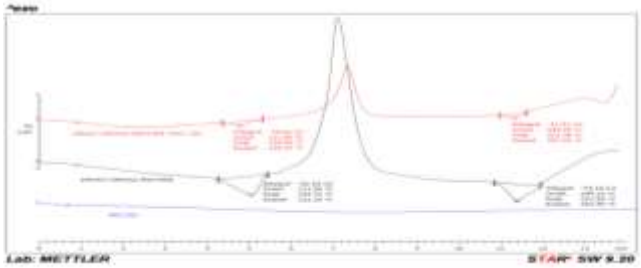


**Fig 9. DSC Thermogram of Drug I, II, MCC PH 102, Drug I, II and MCC PH 102**

**DSC Thermograms Of Magnesium Stearate**

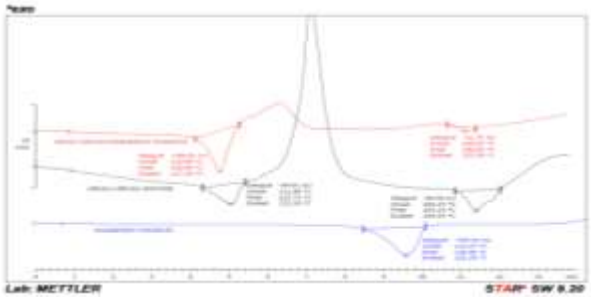


**Fig 10. DSC Thermogram of Drug I, II, Magnesium stearate, Drug I, II and Magnesium stearate**

**DSC thermograms of dextrin**

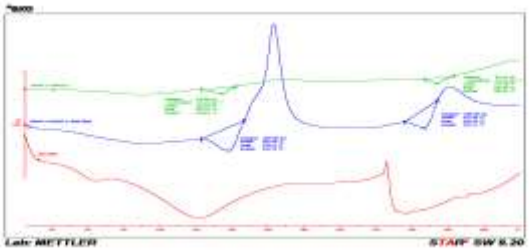


**Fig 11. DSC Thermogram of Drug I, II, Dextrin, Drug I, II and Dextrin**

**DSC Thermograms of EPO**

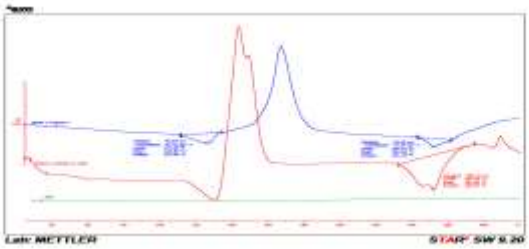


**Figure 12 DSC Thermogram of Drug I, II, EPO, Drug I, II and EPO**

**Physical observation of drug and excipient blends**

**Post Compressional Parameters**

**Fineness of dispersion**

**Inference**

From the above study it was known that nothing remains on the mesh when dispersion passed through the mesh.

**Discussion**

From the above inference it was found that the dispersion formed was passed through the #25 mesh which indicates that the tablets passed the test.

***In-vitro* Dissolution test**

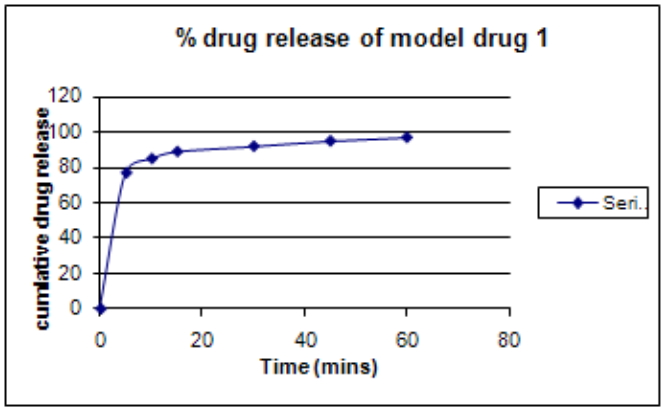
Dissolution is a process by which the disintegrated solid solute enters the solution. The test determines the time required for a definite percentage of the drug in a tablet to dissolve under specified conditions.

**Dissolution Parameters**

| Dissolution Parameters | |
|---|---|
| Medium | 0.1N HCL |
| Apparatus | USP-II apparatus |
| Volume | 900 ml |
| RPM | 50 |
| Temperature | 37 $^0$C±0. 5 $^0$C |
| Sampling times | 5, 10, 15, 30, 45, 60 (For Piperaquine tetra phosohate)<br>5, 10, 15, 30, 45, 60, (for Dihydroartemisinin) |

**Dissolution Profile of Piperquinetetraphosphate**

**Fig 12. Dissolution graph of piperquinetetraphosphate.**




**Dissolution Profile of dihydroartemisinin**

**Calculation and ABSORBANCE, CONC**

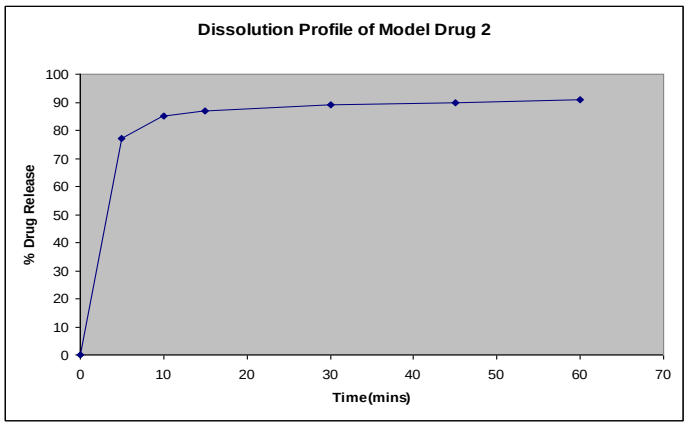



**Fig 13. Dissolution graph of Dihydroartemisinin in 0.1N Hcl Dissolution Profile with EPO**

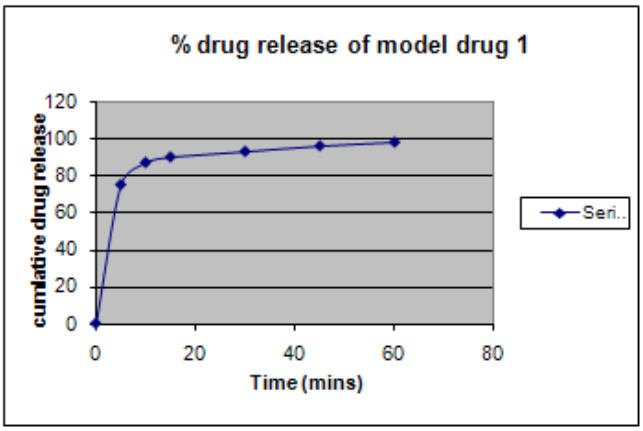



**Fig 14. Dissolution graph of Piperquinetetraphosphate with EPO**

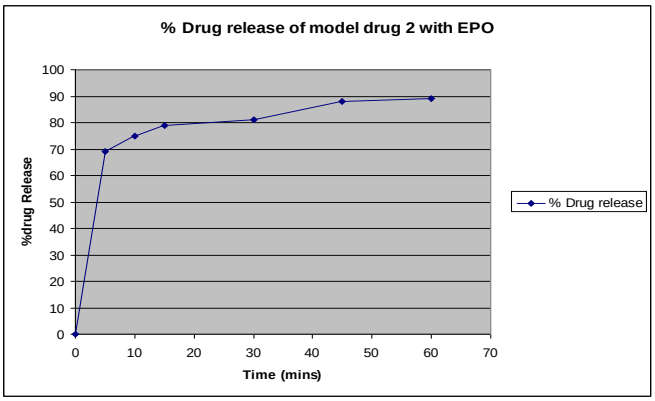



**Fig-15 Dissolution graph of Dihydroartemisinin with EPO**

**Table 37**

| Time(mins) | % Drug release |
|---|---|
| 5 | 77 |
| 10 | 85 |
| 15 | 87 |
| 30 | 89 |
| 45 | 90 |
| 60 | 91 |

**Table 28 Dissolution profile of Piperquinetetraphosphate with EPO**

| Time(mins) | % Drug release |
|---|---|
| 5 | 75 |
| 10 | 87 |
| 15 | 90 |
| 30 | 93 |
| 45 | 96 |
| 60 | 98 |

**Table 39. Dissolution profile of dihydroartemisinin with EPO**

| Time(mins) | % Drug release |
|---|---|
| 5 | 69 |
| 10 | 75 |
| 15 | 79 |
| 30 | 81 |
| 45 | 88 |
| 60 | 89 |

**Inference**

1. It was observed that optimized that optimized formulation with conventional method exhibited More than 85% drug release.at 15 minutes. For drugs 1and drugs 2
2. Optimized formula using polymer coating method exhibited 90% drug release at 15 minutes for model drug but dihydroartemisinin the release was found to be 79% at 15 minutes
3. The end release from the formulations and for both the drugs are found to be comparable

**Summary And Conclusion**

1. Preformulation studies:

a) From the Carr's index and Hausner's ratio the flow property of both the Model drugs is Very poor flow as per the recorded values.

b) From the above solubility it can be concluded that the model drug 1and model drug 2 are having highest solubility in 0.1 N HCL. Compared with other media.

c) Drug-Excipients compatibility studies were performed by physical observation. The physical observations have shown no significant change in the binary mixture of drug and excipients.

2. Formulation development:

a) Formulation development was done using two approaches, taste masking by conventional methodology and taste masking by polymer coating.

b) Eudragit was used as a polymer in taste masking by polymer coating.

c) Different formulations were prepared by using different disintegrants like Sodium starch glycolate , PolyPlasdoneXL, PolyPlasdoneXL10, , Kollidon CL, Ac-di-sol, Pregelatinized starch, Low Hydroxy Propyl Cellulose (LH11), Kollidon CL-M, Low Hydroxy Propyl Cellulose (LH21) .

d) Among all the disintegrants used, crospovidone (kollidon CL) exhibited lower disintegration time than that other disintegrants used

e) Among all the sweeteners used , sucralose was found to be sweet with no agitation

f) Among the all flavors ,Strawberry flavor as found to be pleasant with satisfactory aroma

**Conclusion**

From the above study it is concluded that a stable immediate release dispersible tablets of a drugs could be obtained using 5% Kollidon as disintegrant in extra granular. And aci-di-sol in intra granulation.Taste masking was achieved with two methods ,taste masking by conventional method and taste masking by the polymer coating .the selected sweetening agent is sucralose and the selected flavor strawberry flavor to achieve taste masking with conventional method .To achieve the taste masking with polymer coating Eudragit EPO was selected as polymer ,sucralose as selected as sweeting agent .strawberry flavor selected as flavor

**The future course of the work would be to conduct**

1. Scalability and optimization of developed formulation
2. Optimization of manufacturing process
3. Long term stability
4. In-vivo evaluation

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