APPLICATION OF QUALITY BY DESIGN APPROACH FOR THE OPTIMIZATION OF ORODISPERSE FILM FORMULATION

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ABSTRACT

Objective: The present study was done to understand the effect of formulation variables on the quality of orodispensible films using quality by design (QbD) approach as mentioned in ICH Q8 (R7) guideline.

Methods: A definitive screening design of experiments (DoE) was used to identify and classify the critical formulation variables affecting critical quality attributes (CQA) using 2×2 factorial design. Based on pre-screening study, the critical formulation variables, i.e. concentration of film-forming polymer and plasticizers (propylene glycol and polyethylene glycol 400 [PEG 400]) were kept in the range of 1.5–2.5% w/w and 0.5–1% v/v, respectively. A total of eight laboratory-scale formulations were prepared which were provided by DoE using solvent casting method. These batches were evaluated for CQAs, i.e. mechanical properties such as folding endurance (FD) and disintegration time (DT). Data were analyzed for elucidating interactions between two variables and for providing a predictive model for the process. Finally, the drug was incorporated into optimized batches, and these were evaluated for in vitro dissolution study in simulated saliva (pH 6.8) as well as their mechanical properties.

Results: The results suggested that the concentration of film-forming polymer and plasticizer was critical to manufacture orodispensible film with desired CQA, i.e. mechanical property (FD > 150 folds) and DT (< 60 s). The percent drug release, FD, and DT of optimized Formulation I (hydroxypropyl methylcellulose [HPMC] E5 [2%] and propylene glycol [0.15 mL]) were found to be 82.13±0.26 (in 15 min), 164±2, and 49±1.5 s, respectively, and for optimized Formulation II (HPMCE5 [2%] and PEG 400 [0.15 mL]) was found to be 64.26±2.026 (in 15 min) and 218±6 and 55±4 s, respectively.

Conclusion: From the results, it has been found that the percentage drug release of naratriptan hydrochloride containing propylene glycol as a plasticizer was greater than the formulation containing PEG 400 as plasticizer. From this, we concluded that QbD is very much useful approach to get an optimized formulation in an economic and faster way in comparison to traditional method (hit and trial methods). The futuristic application of the film will involve the management of an acute migraine.

Keywords: Quality by design, Design of experiments, Critical quality attributes, Folding endurance, Naratriptan hydrochloride, Migraine.

INTRODUCTION

In the past few years, the pharmaceutical company or researchers mainly focus on those drug delivery systems, which provide faster onset of action of drug, enhanced bioavailability, and high patient compliance [1]. Nowadays, the best route for the administration of drug is oral as compared to other drug delivery route [2]. From all the dosage forms available in the market, there is a one solid dosage form, i.e. symptomatic therapy which further divided into two, i.e. use of non-specific drugs and specific drugs (ergot alkaloids and triptans), depends on specific drugs and specific drugs (ergot alkaloids and triptans), depends on severe throbbing, pulsating pain often associated with photophobia, phonophobia, nausea, and vomiting. It worsens with day to day activity of patient [9,10]. An untreated migraine attack can past for 4–72 h [11,12]. Sexual dimorphism is reported in migraine, i.e. prevalence ratio among men and women is 3:7 [13,14].

There are two approaches through which we can manage migraine, i.e. symptomatic therapy which further divided into two, i.e. use of non-specific drugs and specific drugs (ergot alkaloids and triptans), depends on severe throbbing, pulsating pain often associated with photophobia, phonophobia, nausea, and vomiting. It worsens with day to day activity of patient [9,10]. An untreated migraine attack can past for 4–72 h [11,12]. Sexual dimorphism is reported in migraine, i.e. prevalence ratio among men and women is 3:7 [13,14].

Acute migraine is a disabling disorder characterized by moderate to severe throbbing, pulsating pain often associated with photophobia, phonophobia, nausea, and vomiting. It worsens with day to day activity of patient [9,10]. An untreated migraine attack can past for 4–72 h [11,12]. Sexual dimorphism is reported in migraine, i.e. prevalence ratio among men and women is 3:7 [13,14].

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on the efficacy of migraine attack. The second approach is preventative therapy, in which doctors give suggestions about daily life routines to patients [15]. There are majorly conventional tablets available in the market, which is used for the management of acute migraine. Our film has more advantages than that as discussed above.

Naratriptan is a serotonin 5-HT$_{1B/1D}$ receptor agonist and is used for the treatment of acute migraine. Activation of 5-HT$_{1B}$ receptor, which is present on the vascular smooth muscles, causes vasoconstriction of smooth muscles [16]. Activation of 5-HT$_{1D}$, which is located on the sensory trigeminal terminals inhibits the release of sensory and vasoactive neuropeptides and vasodilator transmitters [17,18].

**MATERIALS AND METHODS**

Naratriptan hydrochloride was obtained as a gift sample from Apotex Pharmachem Pvt. Ltd., India. Hydroxypropyl methylcellulose (HPMC) E5, propylene glycol, and polyethylene glycol 400 (PEG 400) were purchased from Loba Chemie. All other chemicals and reagents used were of analytical grade.

**Preparation of orodispersible placebo film**

Solvent casting method was used for the preparation of film. In this method initially, all the polymers are dissolved in a suitable solvent, and the drug and other additives are mixed in the other beaker containing a suitable solvent. After that, both solutions are mixed stirring them for some time. Then, the solution is subjected to the sonicator to eradicate the air bubble. Finally, that solution is transferred into a Teflon or glass Petri plate, and then placed in an oven for overnight at 50–60°C for drying. Peel out the film and keep in the desiccator till further use (Fig. 1) [19]. The film was cut in a piece of 3×1 cm$^2$ for further evaluation with the help of a surgical blade.

**QbD approach to develop orodispersible placebo film**

A definitive screening design of experiments (DoE) was used to identify and classify the CPP affecting CQA using 2×2 factorial design. In this research study, we have considered CPP is concentration of HPMC E5, propylene glycol, and PEG 400. From the literature, we get to know about the concentration of above through which, good film was obtained with desired outcomes. If we increase the concentration of polymer, then there would be a problem taking place during pouring, and resulting film is too thick. If we decrease the concentration, film becomes too thin, and it does not give desired outcomes. The main purpose of focusing disintegration time (DT) and folding endurance (FD) as CQA because if the DT is more than 60 s, then there may be chances that the patient may split it. This is the reason we get eight batches after applying DoE (Figs 2 and 3).

**Evaluation of orodispersible placebo film**

**FD**

It is the number of times a film could be folded manually at the same place without getting crack on it. It was checked by folding each film repeatedly at the same place until it breaks or folds it for 150 times whichever is less [20].

**In vitro DT**

It tells about the disintegration and dissolution features of the film. Films from each batch of dimensions 3 cm × 1 cm$^2$ were put in a Petri dish (6.5 cm diameter) having 25 ml of simulated saliva, maintained at 37°C, with agitation every 10 s. The DT was recorded when the film starts to break or disintegrate [21].

**Preparation of optimized orodispersible film containing naratriptan hydrochloride**

After analyzing the observations of 8 batches in DoE (Table 1); finally, we got the optimized concentration of polymer and plasticizer for the final formulation in which we had incorporated naratriptan hydrochloride. Accurately weigh 10 mg of drug and placed into the beaker containing 10 mL of water. Then, the solution was subjected to magnetic stirrer for dissolving the drug completely followed by addition of remaining additives. Further, the procedure was same as discussed above for the preparation of orodispersible placebo film.
**Evaluation of optimized formulation (Table 2)**

**FD and in vitro DT**

The folding endurance (FD) and in vitro disintegration time (DT) studies were performed as per the procedures mentioned under the title - Evaluation of orodispersible placebo film.

| Formulation | HPMC E5 (%w/v) | Propylene glycol (mL) | PEG 400 (mL) |
|-------------|----------------|-----------------------|--------------|
| F1          | 1.5            | 0.1                   | -            |
| F2          | 1.5            | 0.2                   | -            |
| F3          | 2.5            | 0.1                   | -            |
| F4          | 2.5            | 0.2                   | -            |
| F5          | 1.5            | -                     | 0.2          |
| F6          | 2.5            | -                     | 0.1          |
| F7          | 2.5            | -                     | 0.2          |
| F8          | 1.5            | -                     | 0.1          |

Table 3: Composition for preparation of placebo film

FD and in vitro DT

*The folding endurance (FD) and in vitro disintegration time (DT) studies were performed as per the procedures mentioned under the title - Evaluation of orodispersible placebo film.***

**In vitro drug release**

The *in vitro* drug release was carried out in 250 ml of simulated saliva as dissolution medium using USP dissolution apparatus I, maintained at 37±0.5°C with 100 rpm. 10 ml samples were taken at different predetermined time intervals, and the same amount of fresh dissolution medium maintained at same temperature was added to maintain the sink condition in the dissolution vessel. Samples were passed through 0.45 µm membrane filter after suitable dilutions, if required and then analyzed spectrophotometrically. It was conducted 3 times for each film formulation, and the average value was taken [22].

**RESULTS**

The resultant formulation was transparent with a smooth texture. The outcomes of the resultant formulation are being tabulated below:

| Formulation | DT (s) (mean±SD) | FD (No.) (mean±SD) |
|-------------|------------------|-------------------|
| F1          | 40±2             | 135±5             |
| F2          | 42±1             | 164±4             |
| F3          | 50±3             | 223±1             |
| F4          | 55±1             | 112±3             |
| F5          | 50±2             | 192±4             |
| F6          | 70±1             | 19±5              |
| F7          | 57±1             | 350±2             |

**Table 2: Results of prepared placebo films (n=3)**

**Table 3: Comparison between predicted and observed value of optimized formulation of HPMC E5 and Propylene glycol (n=3)**

| Responses | Predicted value | Observed value (mean±SD) |
|-----------|-----------------|--------------------------|
| DT (s)    | 46.75           | 49±1.5                   |
| FD (No.)  | 158.5           | 164±2                    |

**Table 4: Comparison between predicted and observed value of optimized formulation of HPMC E5 and PEG 400 (n=3)**

| Responses | Predicted value | Observed value (mean±SD) |
|-----------|-----------------|--------------------------|
| DT (s)    | 58              | 55±4                     |
| FD (No.)  | 222             | 218±6                    |

**Table 5: In vitro drug release of the film of HPMC E5 and propylene glycol (n=3)**

| Time (min) | Absorbance (mean±SD) | Conc. (µg/mL) (mean±SD) | Corrected conc (µg/mL) (mean±SD) | Amount of drug (mg) (mean±SD) | % drug release (mean±SD) |
|------------|-----------------------|--------------------------|-----------------------------------|-----------------------------|--------------------------|
| 0          | 0                     | 0                        | 0                                 | 0                           | 0                        |
| 2          | 0.10±0.002            | 0.480±0.02               | 0.480±0.02                        | 0.120±0.005                 | 41.29±1.730              |
| 5          | 0.11±0.003            | 0.661±0.03               | 0.671±0.03                        | 0.167±0.007                 | 57.75±2.650              |
| 10         | 0.13±0.001            | 0.783±0.01               | 0.802±0.004                       | 0.20±0.001                  | 69.01±0.340              |
| 15         | 0.14±0.001            | 0.924±0.01               | 0.954±0.006                       | 0.238±0.002                 | 82.13±0.260              |
| 20         | 0.14±0.002            | 0.964±0.02               | 1.021±0.020                       | 0.255±0.005                 | 87.81±1.840              |
| 25         | 0.15±0.002            | 1.035±0.02               | 1.130±0.010                       | 0.282±0.004                 | 97.21±1.980              |
| 30         | 0.16±0.001            | 1.075±0.01               | 1.172±0.010                       | 0.292±0.002                 | 100.82±1.050             |

**Table 3: Comparison between predicted and observed value of optimized formulation of HPMC E5 and Propylene glycol (n=3)**

**Table 4: Comparison between predicted and observed value of optimized formulation of HPMC E5 and PEG 400 (n=3)**

**Table 5: In vitro drug release of the film of HPMC E5 and propylene glycol (n=3)**

**CONCLUSION AND DISCUSSION**

From the literature review, we came to know that using the concentration of polymer between 1.5% w/v and 2.5% w/v and plasticizer 0.1–0.2 mL, we will get the required FD, i.e. >150 folds and DT <1 min. We used same concentration of polymer and plasticizer, after that applied QbD. After applying QbD, we got an optimized formulations which show the required outcomes, i.e. FD >150 folds and DT <1 min (Table 3 and 4). We had done the *in vitro* dissolution study of both optimized batches, and from the results (Table 5 and 6), it had been concluded the percentage drug release of naratriptan hydrochloride in the optimized Formulation I after 15 min was >80% (Fig. 4). Hence, from this, we selected Formulation I for further study. From this, we concluded that QbD is very much useful approach to get an optimized formulation.

**Table 1: Composition for preparation of placebo film**

**Table 2: Results of prepared placebo films (n=3)**

**Table 3: Comparison between predicted and observed value of optimized formulation of HPMC E5 and Propylene glycol (n=3)**

**Table 4: Comparison between predicted and observed value of optimized formulation of HPMC E5 and PEG 400 (n=3)**

**Table 5: In vitro drug release of the film of HPMC E5 and propylene glycol (n=3)**

**Results**

The resultant formulation was transparent with a smooth texture. The outcomes of the resultant formulation are being tabulated below:

Optimized Formulation I contains the drug, hydroxypropyl methylcellulose (HPMC) E5 and propylene glycol, optimized Formulation II contains the drug, HPMC E5, and polyethylene glycol 400
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Table 6: *In vitro* drug release of the film of HPMC E5 and PEG 400 (n=3)  

| Time (min) | Absorbance (mean±SD) | Conc. (μg/mL) (mean±S.D.) | Corrected conc (μg/mL) (mean±SD) | Amount of drug (mg) (mean±SD) | % drug release (mean±SD) |
|-----------|----------------------|---------------------------|-------------------------------|-------------------------------|-------------------------|
| 0         | 0                    | 0                         | 0                             | 0                             | 0                       |
| 2         | 0.095±0.003          | 0.4195±0.030              | 0.4195±0.030                  | 0.1048±0.007                  | 32.74±2.380             |
| 5         | 0.110±0.002          | 0.5778±0.020              | 0.5861±0.021                  | 0.1465±0.005                  | 45.74±1.716             |
| 10        | 0.120±0.010          | 0.6720±0.010              | 0.6919±0.011                  | 0.1729±0.002                  | 53.99±0.871             |
| 15        | 0.132±0.002          | 0.7931±0.020              | 0.8479±0.021                  | 0.2065±0.005                  | 64.26±2.026             |
| 20        | 0.144±0.003          | 0.9142±0.030              | 0.9634±0.031                  | 0.2408±0.008                  | 75.18±2.499             |
| 25        | 0.160±0.002          | 1.0754±0.020              | 1.1427±0.022                  | 0.2856±0.005                  | 89.17±1.745             |
| 30        | 0.172±0.001          | 1.196±0.010               | 1.2851±0.012                  | 0.3213±0.003                  | 100.32±1.018            |

SD: Standard deviation, HPMC: Hydroxypropyl methylcellulose, PEG 400: Polyethylene glycol 400