Development and optimisation of novel oral formulation of an opioid analgesic using central composite design

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Abstract: Introduction of matrix type sustained release systems were a breakthrough for novel oral drug delivery systems. Present research focuses on the development and evaluation of Fentanyl citrate sustained release formulations. It is a potent, sparingly soluble synthetic opioid analgesic with rapid onset and short duration of action. Considering the half-life of the drug which is 1.5 h, there is a strong clinical need and market potential for delivery systems that will deliver drug in controlled and prolonged manner. A number of strategies were planned for formulation development and evaluation such that they demonstrate robust stability and in vitro-in vivo performance using putative hydrophilic polymer HPMC (HPMCK 15M) in combination with hydrophobic polymer Ethyl cellulose N10. A Central composite design was employed to get an optimum formulation suitable for once a day administration. Effects of formulation variables, hydrodynamic conditions and agitational variations on drug release profile were also investigated. Drug release mechanisms

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The developed matrix tablets were successfully prepared without the need for functional coating, thus promising to be a cost effective formulation with high commercial probability.

PUBLIC INTEREST STATEMENT

Oral drug delivery system has always been a convenient dosage form both to the patient as well as to pharmaceutical manufacturer because of its simplicity in drug administration and ease of production, batch scale up respectively. The present research project aims at developing sustained release oral uncoated tablet of Fentanyl citrate for chronic pain management. This tablet would be more patient compliant as it has to be taken once a day. Being a sustained release tablet, it would be resulting in less dose frequency, will also help to maintain the desired amount of drug in body for longer time needed to relieve the pain therefore making it convenient to treat the chronic illness patients. It may also be cost effective as the coating process is not required and still the product is used only once a day. The polymers used to prepare the tablet works on swelling mechanism which allows tailor made release of drug at slower rate suitable to give one tablet per day.
using various mathematical kinetic models are discussed. The developed matrix tablets were successfully prepared without the need for functional coating thus promising to be a cost effective formulation with high commercial probability.

**Subjects: Health and Social Care; Allied Health**

**Keywords:** matrix system; opioid; analgesic; sustained release; oral delivery; factorial design; central composite

1. Introduction

Sustained release matrix tablets are relatively easy to fabricate by incorporating drug molecules in slowly disintegrating or inert porous materials, versatile, effective and at low cost (Basak, Reddy, & Mani, 2006; Kumar, Bhowmik, Srivastava, Paswan, & Dutta, 2012; Patel, Panchal, Patel, Brahmbhatt, & Suthar, 2011). These delivery systems are designed to achieve therapeutically effective concentrations of drug in the systemic circulation over an extended period of time, thus achieving better patient compliance and allowing reduction of both the total dose of drug administered and the incidence of adverse effects (Perucca, 2009). The goal in designing sustained or controlled delivery systems is to reduce frequency of dosing or to increase the effectiveness of the drug by localization at the site of action, reducing the dose required, providing uniform drug delivery (Dixit, Maurya, & Sagar, 2013; Kube Rahul et al., 2015). Among the different approaches studied, matrix systems still appear as one of the most attractive forms, from economic as well as process development and scale-up points of view (Ravi Kumar & Kumar, 2001). Moreover, it has been studied that the suitable combination of a variety of polymers as matrix-forming materials enables appropriate modifications of the release characteristics of the drug from the dosage form (Amaral, Lobo, & Ferreira, 2001). Drug release rate from the dosage form is controlled mainly by the nature and proportion of polymer used in the preparations without the need for complex procedures such as coating and pelletization. Hydrophilic polymer matrix is widely used in case of sustained release formulations of water insoluble drug (Reddy, Mutalik, & Reddy, 2003). Polymers used for matrix tablets may be classified as hydrogels, soluble polymers, biodegradable polymers, Non-biodegradable polymers, mucoadhesive polymers, and natural gums (Dash & Verma, 2013; Digambar Mali et al., 2015). Research studies demonstrate Hydroxypropyl methyl cellulose (soluble polymers) as the most common hydrophilic polymer used to prolong drug release due to its rapid hydration, good compression and gelling characteristics along with its ease of use, availability and very low toxicity (Ravi Kumar & Kumar, 2008; Sandhan, Sapra, & Mor, 2013). Controlled swelling and cross-linking are the utmost important parameters for its retarding action. In the development of a sustained release tablet, major challenge is to design an optimized formulation with an appropriate dissolution rate in a short time period and minimum number of trials. Many statistical experimental designs have been recognized as useful techniques to optimize the process variables. For this purpose, a computer based optimization technique with a response surface methodology (RSM) utilizing a polynomial equation has been widely used (Singh, Dahiya, Saharan, & Ahuja, 2005a). The technique requires minimum experimentation and time, thus proving to be far more effective and lucrative than the conventional methods of formulating sustained release dosage forms (Singh, Dahiya, Saharan, & Ahuja, 2005b).

Fentanyl citrate is a parenterally administered opioid used in the management of chronic pain (Xiao, Naso, & Bennett, 2008). It is a sparingly soluble drug and is slowly and incompletely absorbed from the gastrointestinal tract. An obstacle to more successful use of this opioid is the high incidence of concomitant gastrointestinal symptoms, such as abdominal discomfort, nausea, and diarrhoea that especially occur during the initial weeks of treatment. Also the compound has relatively short plasma elimination half-life of 1.5–4.5 h. The side effects and the need for frequent administration which is two or three times per day when larger doses are required can cause non-compliance. So there is call to develop SR formulation of the drug to prolong its duration of action and to improve patient compliance. The research work thus aimed at developing once a day sustained release drug delivery system of fentanyl citrate using combination of hydrophilic and hydrophobic polymers. HPMCK 15M, a hydrophilic polymer ( Hiremath, 2007) forms firm gel from which the drug
diffusion may take place easily. Ethyl cellulose, hydrophobic polymer does not form gel allowing the drug diffusion to take place at slower rate. Ethyl cellulose does not erode so the concentration of the polymer required to retard the drug release is low. Permeability of the matrix could be modified using admixture of HPMC with ethyl cellulose (Ara, Sharma, Bhat, Bhandari, & Samieh, 2014). Hence, in the present research work attempts were made to develop sustained release matrix tablets of drug using putative hydrophilic matrix material HPMC (HPMCK 15M) in combination with hydrophobic polymer Ethyl cellulose N10 (Dashevsky & Mohamad, 2006) and to study the in vitro release characteristics and release rate kinetics of the prepared formulations. The kinetics of the dissolution process was investigated by application of two kinetic equations viz. Koresmeyer Peppas equation and Higuchi square root equation. A Central composite design (CCD) was employed to get an optimized formulation suitable for once a day administration (Singh, Pahuja, Kapil, & Ahuja, 2009).

2. Materials and methods

2.1. Materials
Fentanyl citrate was procured from Rusan Pharma, Mumbai, India under Test License (Form 29) and Transport permit from FDA. Microcrystalline cellulose and ethyl cellulose N10 were obtained as gift samples from Signet Chemicals and Umang Pharma (Mumbai). HPMCK 15M was provided as gift sample from Colorcon Pvt. Ltd. (India). All inactives were purchased from authentic suppliers. They were standardized as per the certificate of analyses.

2.2. Methods
Sustained release matrix formulations of the opioid were prepared by wet granulation technique depicted in Figure 1. Different trial formulations were prepared using varying combinations of HPMCK 15M and Ethyl cellulose as release controlling polymers with fixed quantity of talcum and magnesium stearate as lubricants, MCC was used as diluent Table 1. Prior to tablet compression, the granules were evaluated for various IPQC parameters.

2.2.1. Characterization of developed sustained release formulations (M1 to M13)

2.2.1.1. Characterization of pre-compression and post-compression parameters. The granules were prepared by wet granulation method (Figure 1) and were evaluated for their pre-compression parameters such as bulk density, tapped density, compressibility index, angle of repose and Hausner’s ratio Table 2. The tapping method was used for the determination of the pre-compression parameters. The tablets were evaluated for their post compression parameters such as weight variation, hardness and friability Table 3.
Table 1. Composition of fentanyl citrate sustained release matrix tablets

| Batch | Fentanyl citrate | HPMCK 15M | Ethyl cellulose N10 | Talc | Magnesium stearate | Microcrystalline cellulose |
|-------|------------------|-----------|---------------------|------|---------------------|--------------------------|
| M1    | 2.5              | 25        | 12.5                | 1.25 | 1.25                | 196.25                   |
| M2    | 2.5              | 25        | 25                  | 1.25 | 1.25                | 195                      |
| M3    | 2.5              | 25        | 37.5                | 1.25 | 1.25                | 182.5                    |
| M4    | 2.5              | 50        | 12.5                | 1.25 | 1.25                | 182.5                    |
| M5    | 2.5              | 50        | 25                  | 1.25 | 1.25                | 170                      |
| M6    | 2.5              | 50        | 37.5                | 1.25 | 1.25                | 157.5                    |
| M7    | 2.5              | 75        | 12.5                | 1.25 | 1.25                | 157.5                    |
| M8    | 2.5              | 75        | 25                  | 1.25 | 1.25                | 145                      |
| M9    | 2.5              | 75        | 37.5                | 1.25 | 1.25                | 132.5                    |
| M10   | 2.5              | 50        | 25                  | 1.25 | 1.25                | 170                      |
| M11   | 2.5              | 50        | 1.25                | 1.25 | 170                 |
| M12   | 2.5              | 50        | 25                  | 1.25 | 170                 |
| M13   | 2.5              | 50        | 25                  | 1.25 | 170                 |

Table 2. Pre-compression parameters (M1–M13)

| Parameters | M1 | M2 | M3 | M4 | M5 | M6 | M7 | M8 | M9 | M10 | M11 | M12 | M13 |
|------------|----|----|----|----|----|----|----|----|----|-----|-----|-----|-----|
| Bulk density (g/ml) | 0.58 | 0.46 | 0.39 | 0.47 | 0.45 | 0.43 | 0.41 | 0.46 | 0.37 | 0.40 | 0.47 | 0.48 | 0.44 |
| Tapped density (g/ml) | 0.66 | 0.54 | 0.48 | 0.56 | 0.55 | 0.57 | 0.59 | 0.57 | 0.47 | 0.52 | 0.53 | 0.55 | 0.51 |
| Compressibility index | 12.5 | 13.7 | 14.5 | 13.2 | 13.6 | 14.1 | 13.5 | 13.4 | 14.1 | 13.9 | 13.2 | 13.6 | 13.8 |
| Hausner's ratio | 1.3 | 1.35 | 1.44 | 1.32 | 1.37 | 1.49 | 1.36 | 1.41 | 1.37 | 1.38 | 1.41 | 1.31 | 1.38 |

Table 3. Post-compression parameters (M1–M13)

| Parameters | Weight variation | Hardness (kp) | Friability (%) | Drug content uniformity |
|------------|------------------|---------------|----------------|-------------------------|
| M1         | Passes           | 6.0–8.0       | 0.15           | 98.9 ± 0.06             |
| M2         |                  |               | 0.21           | 100.7 ± 0.08            |
| M3         |                  |               | 0.23           | 101.5 ± 0.03            |
| M4         |                  |               | 0.18           | 101.2 ± 0.07            |
| M5         |                  |               | 0.2            | 100.3 ± 0.6             |
| M6         |                  |               | 0.23           | 99.9 ± 0.04             |
| M7         |                  |               | 0.19           | 100.3 ± 0.02            |
| M8         |                  |               | 0.16           | 99.4 ± 0.09             |
| M9         |                  |               | 0.18           | 101.4 ± 0.07            |
| M10        |                  |               | 0.19           | 100.2 ± 0.01            |
| M11        |                  |               | 0.21           | 99.8 ± 0.05             |
| M12        |                  |               | 0.22           | 100.1 ± 0.03            |
| M13        |                  |               | 0.19           | 99.9 ± 0.04             |
2.2.1.1. **Tablet assay.** Tablets (20 in number) were taken and crushed to powder. Exact amount of powder (average weight, 250 mg) was weighed and diluted up to 200 ml with phosphate buffer pH 6.8. After sonication the solution for 15 Min, it was filtered through 0.45 μm filter paper. The drug content in the tablets was analyzed after appropriate dilution of test solution using the developed and validated HPLC method.

2.2.1.2. **In vitro drug release studies.** Drug release from 6 tablets of each formulation, in triplicate, was determined using the USP II Electrolab dissolution test apparatus. The studies were conducted by pH change method using 250 ml of 0.1 N HCl for first two hours followed by 250 ml of phosphate buffer up to 24 h maintained at 37 ± 0.5°C at 50 rpm. Then 5 ml of aliquots were withdrawn at 2, 4, 6, 8, 12 and 24 h with replacement of fresh media. Sample solutions were analyzed by validated high performance liquid chromatography (HPLC) method. The in vitro drug release profiles were studied and are as shown in Figure 2 and reported in Table 4.

2.2.1.3. **Drug release kinetics.** In order to propose the possible release mechanism, drug release data was fitted to various mathematical models such as zero order, first order, Higuchi and Korsmeyer equations.

2.2.2. Optimization of developed sustained release matrix systems of fentanyl citrate using CCD based on design expert 8.0 software

2.2.2.1. **Experimental design and statistical analysis.** A CCD with α:1 was employed as per the standard protocol to get an optimized formulation. Amount of HPMCK 15M (A) and Ethyl cellulose (B) were selected as the Independent variable factors, studied at 3 levels each. All other formulation and process variables were kept invariant throughout the study. Table 5 summarizes an account of

![Figure 2. Cumulative drug release (%) vs. time profiles as per the experimental design for formulations, (a) M1–M6; (b) M7–M13; (c) Cumulative drug release (%) vs. time profile of selected formulation M9.](image)

Note: Each value represents the mean ± SD, n = 6.

### Table 4. In vitro release profiles of developed formulations (M1–M13)

| % Drug released | Time (hr) | M1 | M2 | M3 | M4 | M5 | M6 | M7 | M8 | M9 | M10 | M11 | M12 | M13 |
|-----------------|----------|----|----|----|----|----|----|----|----|----|-----|-----|-----|-----|
| % Drug released |          | 1  | 2  | 4  | 6  | 8  | 12 | 24 |    |    |     |     |     |     |
| % Drug released |          | 24.5 | 23.6 | 22.5 | 21.2 | 23.2 | 20.2 | 22.1 | 17.5 | 20.5 | 22.6 | 20.2 | 19.2 |
| % Drug released |          | 36.5 | 35.3 | 33.2 | 32.1 | 30.6 | 31.2 | 31.2 | 28.3 | 26.4 | 29.8 | 30.2 | 30.1 | 28.9 |
| % Drug released |          | 44.2 | 42.3 | 40.3 | 41.2 | 42.1 | 38.6 | 40.2 | 38.4 | 38.4 | 40.5 | 42.3 | 39.5 | 41.4 |
| % Drug released |          | 49.2 | 47.6 | 45.8 | 49.3 | 48.7 | 43.5 | 46.5 | 44.1 | 42.3 | 46.7 | 49.8 | 47.3 | 47.8 |
| % Drug released |          | 72.5 | 70.9 | 69.8 | 70.5 | 71.2 | 55.4 | 70.6 | 58.7 | 45.3 | 70.3 | 69.6 | 70.4 | 71.8 |
| % Drug released |          | 85.6 | 84.5 | 82.6 | 76.4 | 77.5 | 73.2 | 75.8 | 65.3 | 52.4 | 77.8 | 80.5 | 76.7 | 78.4 |
| % Drug released |          | 99.9 | 99.13 | 99.19 | 100.2 | 100.3 | 85.6 | 99.8 | 96.2 | 88.7 | 100.5 | 100.8 | 100.5 | 100.4 |
Table 5. Factor combinations of independent variables as per chosen experimental design

| Trial No. | Coded independent variables factor levels |
|-----------|------------------------------------------|
|           | A      | B      |
| 1         | −1     | −1     |
| 2         | −1     | 0      |
| 3         | −1     | 1      |
| 4         | 0      | −1     |
| 5         | 0      | 0      |
| 6         | 0      | 1      |
| 7         | 1      | −1     |
| 8         | 1      | 0      |
| 9         | 1      | 1      |
| 10        | 0      | 0      |
| 11        | 0      | 0      |
| 12        | 0      | 0      |
| 13        | 0      | 0      |

Translation of coded levels in actual units

| Code | A: HPMCK 15 M (mg)/(%) | B: Ethyl cellulose N10 (mg)/(%) |
|------|------------------------|-------------------------------|
| −1   | 25/(10%)               | 12.5/(5%)                     |
| 0    | 50/(20%)               | 25/(10%)                      |
| 1    | 75/(30%)               | 37.5/(15%)                    |

Response variables

|     |                          |
|-----|--------------------------|
| Y1  | Percent of drug released in 2 h |
| Y2  | Percent of drug released in 12 h |
| Y3  | Percent of drug released in 24 h |
| Y4  | 50% drug released in (T50, %) |

13 experimental runs studied, their factor combinations, and the translation of the coded levels to the experimental units employed during the study, (Y1) % of drug released in 2 h (rel2 h), Y2 % of drug released in 12 h (rel12 h), Y3 % of drug released in 24 h (rel24 h) and Y4 time for 50% drug release were taken as the response variables.

Various RSM computations for current optimization study were performed employing Design Expert software (Design Expert trial version 8.0 State- ease Inc, Minneapolis, MN). Polynomial models including interactions and quadratic terms were generated for all the response variables using multiple linear regression (MLRA). The general form of the MLRA model is represented as the following equation:

$$y = \beta_0 + \beta_1 A + \beta_2 B + \beta_3 A_1 B_2 + \beta_4 A^2 + \beta_5 B^2 + \beta_6 A B^2 + \beta_7 A^2 B$$

where \(\beta_0\) is the intercept representing the arithmetic average of all quantitative outcomes of 13 runs; \(\beta_1, \beta_2, \beta_3, \beta_4, \beta_5, \beta_6, \) and \(\beta_7\) are the coefficients computed from the observed experimental response values of Y; A and B are the coded levels of the independent variable(s). The term \(A_1 B_2\) and \(A^2 (i = 1–2)\) represent the interaction and quadratic terms, respectively, statistical validity of the polynomials was established on the basis of ANOVA provision in the Design Expert software. Two dimensional (2-D) Contour plots, Figures 3 and 4 were constructed based on the model polynomial functions using Design Expert software. These plots are very useful to see interaction effects of the factors on the responses.
3. Results and discussions

3.1. Physicochemical characterization of pre-compression and post compression parameters

Formulation of granules is a prerequisite in the production of tablets by wet granulation method. Physical parameters such as surface hardness, surface characteristics can significantly affect the rate of dissolution of drug from the complex system. The selection of wet granulation technique for preparation of the matrix tablets was based on previously reported study which suggested that wet granulation results in harder tablets with lower matrix porosity that gives very low release rates as compared to direct compression. In our study, ethyl alcohol was used as granulating agent. Non aqueous granulating agent was used with a deliberation to avoid the use of water and subsequent use of heat for drying the granules.

3.1.1. Pre-compression granule mix parameters

The granules of different formulations were evaluated for the pre-compression parameters and their results are given in Table 2. It was observed that as the concentration of ethyl cellulose was increased the bulk densities and tapped densities of granules were found to be high. Generally, values of compressibility index up to 15 indicate good to excellent flow properties however value above 25% indicate poor flow ability. The values of compressibility index were found to be within acceptable limits for all the formulations. However, compressibility index was higher for formulation with high amount of HPMC and Ethyl cellulose. All results in Table 2 indicate that the formulated granules possessed satisfactory flow properties and compressibility.
3.1.2. Post compression parameters: USP

The compressed tablets were evaluated for their post compression parameters and the results are listed in Table 3. All the post compression parameters were found to be within official standards. The fabricated tablets were found to be of acceptable quality. The drug content in all the developed formulations varied between 99.8 and 101.2% (mean 100.6%).

3.2. Optimization of developed sustained release matrix Systems of Fentanyl citrate using CCD using Design Expert 8.0 Software

The formulations were optimized using the CCD. Various formulations, M1–M13. Table 1 were prepared as per the design, Table 5. The results of dissolution studies are tabulated in the Table 5 with the in vitro release profiles depicted in Figure 2(a) and (b). Table 6 lists the selective dissolution parameters computed as per the experimental design. The effect of the two independent variables (HPMCK 15M and Ethyl Cellulose N10) was studied based on these parameters as dependent response variables.

Table 6. Drug release parameters of various trial formulations as per CCD experimental design

| Trial No. | Factorial amount (mg) | Rel1 h (%) | Rel12 h (%) | Rel24 h (%) | T50% (h) | N  | K_h  | R^2 |
|-----------|-----------------------|------------|-------------|-------------|----------|----|------|-----|
| M1        | 25 12.5               | 36.5       | 85.6        | 99.9        | 6.03     | 0.49| 31.21| 0.992|
| M2        | 25 25                 | 35.3       | 84.5        | 99.13       | 6.54     | 0.501| 32.23| 0.997|
| M3        | 25 37.5               | 33.2       | 82.6        | 99.19       | 6.82     | 0.512| 31.11| 0.998|
| M4        | 50 12.5               | 32.1       | 76.4        | 100.2       | 6.87     | 0.525| 32.18| 0.999|
| M5        | 50 25                 | 30.6       | 77.5        | 100.3       | 7.12     | 0.547| 33.23| 0.997|
| M6        | 50 37.5               | 31.2       | 73.2        | 85.6        | 7.32     | 0.519| 29.98| 0.991|
| M7        | 75 12.5               | 31.2       | 75.8        | 99.8        | 7.73     | 0.58 | 34.24| 0.99|
| M8        | 75 25                 | 28.3       | 65.3        | 96.2        | 7.52     | 0.53 | 30.11| 0.98|
| M9        | 75 37.5               | 26.4       | 52.4        | 88.7        | 11.5     | 0.53 | 24.56| 0.995|
| M10       | 50 25                 | 29.8       | 77.8        | 100.5       | 7.12     | 0.586| 33.78| 0.998|
| M11       | 50 25                 | 30.2       | 80.5        | 100.8       | 6.99     | 0.553| 32.17| 0.999|
| M12       | 50 25                 | 30.1       | 76.7        | 100.5       | 6.74     | 0.582| 33.87| 0.998|
| M13       | 50 25                 | 28.9       | 78.4        | 100.4       | 6.78     | 0.5998| 34.23| 0.999|

Figure 2(a) and (b) exhibits the mean (±SD) cumulative drug release (%) vs. time profiles obtained for various formulations, prepared as per CCD. From the comparative in vitro studies, it was observed that formulation M1, with low levels of HPMCK 15M and Ethyl cellulose N10, more than 80% drug was released in 12 h. This indicated that low level of the polymer is not sufficient to sustain the drug for prolonged period. Thus formulation M2 was prepared with low levels of HPMCK 15M and medium levels of ethyl cellulose N10. There was no significant difference observed in the release profile as compared to formulation M1. The formulation M3 with low levels of HPMCK 15M and high levels of Ethyl cellulose N10 showed release profile slightly sustained 3–4% less than M1 and M2 throughout the dissolution runs. Thus from in vitro release studies of formulations M1, M2, M3, Figure 2(a) it was evident that low level of ethyl cellulose had less pronounced effect than HPMCK 15M with low level. It also indicated the use of high concentration of ethyl cellulose in order to attain the desired release profile. Formulations M4, M5 were prepared with medium levels of HPMCK 15M and low and medium levels of ethyl cellulose respectively. From the in vitro release profile of formulation M4, it was observed that it showed similar release pattern as that of formulation M3 up to 12 h. However, at 12 h it could retard the drug release comparatively more than M3 i.e. it showed a difference of 6% as compared to formulation M3. The effect of ethyl cellulose N10 was comparatively less significant than HPMCK 15M when used at medium level. As seen from the release profile of formulation M5, Figure...
2(b), here the concentration of HPMCK 15M used was same i.e. medium level as that used in formulation M4. In formulation M5 the concentration of ethyl cellulose was however increased from low to medium. On comparison of these two formulations M4 and M5, there was no significant difference observed in their release profiles. Formulation M6 was prepared with medium level of HPMCK 15M and high level of ethyl cellulose N10. In comparison to formulation M5, it exhibited similar release pattern up to two hours with 1–2% difference in the amount of drug release till 6 h. At 8 h there was a significant difference observed between these two formulations (approx 20%). The in vitro release studies confirm that both the polymers had antagonistic effect on the drug release. Among all the formulations (M1–M13), formulation M9 was the formulation showing the desired release profile suitable for once a day administration i.e. 15.9% in 1 h, 38.4% in 4 h, 45.3% in 8 h, 52.4% in 12 h and 88.7% in 24 h, Figure 2(c). Total amount of drug released from all the formulations (M1–M13) up to 12 h ranged between 52.4 and 85.6% indicating an incomplete drug release at higher concentration of HPMCK 15M as well as ethyl cellulose. Rate of drug release (until 12 h) tended to decrease with increase in the content of either HPMCK 15M or ethyl cellulose as seen from comparative in vitro release profiles of formulations M3–M9, this part of work is in line with literature findings that the viscosity of gel layer around the tablets increases with increase in the hydrogel concentration, thus limiting the release of active ingredient. The gel formed during the penetration of dissolution media into matrix structure, consists of closely packed swollen particles. With further increase in polymer amount, thicker gel is formed that strongly inhibits the penetration of dissolution media, resulting in significant reduction in the values of rel, indicating slower drug release. The values of $T_{50\%}$ enhanced markedly from 6.03 h observed at low levels of both the variables (Formulation M1) to as high as 11.5 h. (Formulation M9) observed at high levels of both the variables. These findings indicated considerable release retarding potential of the two polymers used in combination.

The formulations with lower levels of two polymers exhibited initial burst in drug release (Formulations M1, M2). This result could be attributed to the dissolution of drug present initially at the surface of the matrices and rapid penetration of dissolution media to the matrix structure. However, the formulations showed little burst effect at higher polymer levels, ratifying better control of drug release. Overall, all the formulations showed quite regulated drug release from 4 h onwards.

### 3.3. RSM optimization results: Mathematical modelling

Mathematical relationships generated using MLRA for the studied response variables are expressed as Equation (a–d).

#### 3.3.1. Statistical equations as per mathematical modeling for dependent response variables

(a) For 2 h drug release

(i) Final equation in terms of coded factors:

\[
Y_1 = +30.16 - 3.50A - 0.45B - 0.37AB - 1.06A^2 + 0.91B^2 - 1.58A^2B + 0.47AB^2
\]

(b) For 12 h drug release

(ii) Final equation in terms of coded factors:

\[
Y_2 = +77.82 - 9.87A - 4.93B - 5.10AB - 2.03A^2 - 2.13B^2
\]

(c) For 24 h drug release

(iii) Final equation in terms of coded factors:
% drug release 24 h, \( Y_3 = +99.76 - 1.46A - 5.82B - 2.60A^2 - 0.25A^2B - 3.54B^2 + 2.87A^4B - 1.18A^3B^2 \)

(d) For \( T_{50\%} \) drug release

(iv) Final equation in terms of coded factors:

\( T_{50\%} \) drug release, \( Y_4 = +6.83 + 0.49A + 0.23B + 0.74A^2B + 0.49A^2 + 0.55B^2 + 0.91A^2B + 1.11A^*B^2 \)

### 3.3.2. Response surface analysis

Figures 3 and 4 are the two dimensional contour plots for the investigated response properties viz. rel\(_{2\ h}\), rel\(_{12\ h}\), rel\(_{24\ h}\) and \( T_{50\%} \). These contour plots depict the interaction between the independent variables and their effects on dependent variables. Figure 3(a) exhibits that the rel\(_{1\ h}\) varied in non-linear fashion, but in descending pattern with an increase in the amount of the two polymers. It also shows that HPMCK 15M has a comparatively greater influence on the response variables than ethyl cellulose. In contrast to the results of drug release in 2 h, contour plot for drug release in 12 h. Figure 3(b) reveals that rel\(_{12\ h}\) varies in somewhat linear fashion with increase in concentrations of both the polymers. However, the effect of HPMCK 15M seems to be pronounced as compared to ethyl cellulose for rel\(_{12\ h}\). But at rel\(_{24\ h}\), Figure 4(a) the effect of ethyl cellulose seems to be more as compared to HPMCK 15M.

Figure 4(b) exhibits that time to 50% drug release \( (T_{50\%}) \) varied in a non-linear fashion, but in an ascending pattern with an increase in the amount of each variable. But at higher concentration of HPMCK 15M and ethyl cellulose the contour turns to be linear. For estimation of significance of the model, the analysis of variance (ANOVA) was carried out as per the provision of design expert software, Table 7 using 5% significance level, a model is considered significant if the \( p \) value (significance probability value) is less than 0.05. From the \( p \)-values presented in Table 7, it can be concluded that for all four responses, the cross product contribution \( (AB) \) and quadratic contributions \( (A^2, B^2, A^2B, B^2A) \) of the model were not significant. But the linear contribution \( (A \) and \( B) \) for all four responses is significant. The polynomial equations compromised the coefficients for intercept, first order effects, interaction terms and high order effects. The sign and magnitude of the main effects signify the relative influence of each factor on the response. The value obtained for main effects of each factor from equations (a, b, d) reveal that HPMCK 15M has pronounced effect on all response values. This is very clearly depicted in Figures 3(a), 4(a) and (b). However, from equation c it can be revealed that at 24 h drug release response, ethyl cellulose has comparatively more pronounced effect individually as compared to HPMCK 15M as seen from Figure 4(a). At a given set of factor levels, however, these higher order polynomials yield results as the net effect of all the coefficients contained in the polynomial.

### Table 7. Analysis of variance (ANOVA) for all four responses

| Source | \( \text{Rel}_{1\ h} (Y_1) \) | \( \text{Rel}_{12\ h} (Y_2) \) | \( \text{Rel}_{24\ h} (Y_3) \) | \( T_{50\%} \) |
|--------|----------------|----------------|----------------|---------|
| Model  | 17.13          | 50.5           | 7.35           | 23.55   |
|        | 0.0032         | 0.0002         | 0.0216         | 0.0015  |
| A      | 33.72          | 71.89          | 10.8           | 3.84    |
|        | 0.0021         | 0.0004         | 0.3466         | 0.1073  |
| B      | 0.56           | 1.99           | 17.02          | 0.81    |
|        | 0.4889         | 0.2167         | 0.0091         | 0.4093  |
| AB     | 0.77           | 40.58          | 6.78           | 17.77   |
|        | 0.4192         | 0.0014         | 0.0480         | 0.0084  |
| A\(^2\) | 4.25           | 4.45           | 0.044          | 5.26    |
|        | 0.0944         | 0.0884         | 0.8426         | 0.0703  |
| B\(^2\) | 3.13           | 4.90           | 8.68           | 6.76    |
|        | 0.1373         | 0.0776         | 0.0320         | 0.0483  |
| A\(^2\)B | 4.55           | 13.00          | 2.75           | 8.93    |
|        | 0.0860         | 0.0154         | 0.1579         | 0.0305  |
| A\(^2\)B | 0.41           | 0.083          | 0.47           | 13.03   |
|        | 0.5483         | 0.7846         | 0.5241         | 0.0154  |
3.3.3. Drug release kinetics

To know the mechanism of drug release from the trial formulations, the data was treated according to Higuchi equation (cumulative percentage of drug released pattern with an increase in the amount of each variable, square root of time) and Korsmeyer et al. (log cumulative percentage of drug released vs. log time) equations. In the experiments conducted, the in vitro release profiles of drug from all the formulations could be best expressed by Higuchi equation as the plots showed high linearity ($R^2$: 0.991–0.999, with $K_H$: 24.56–34.24) as shown in Table 8. In the current study, the values of release rate exponent ($n$) calculated as per the equation proposed by Koresmeyer et al. ranged between 0.4898 and 0.5998 (Table 8). For matrix tablets, an $n$ value of near 0.5 indicates diffusion control, and $n$ value of near 1.0 indicates erosion or relaxation control. Intermediate values suggest that diffusion and erosion contribute to the overall release mechanism. In our experiments the results of $n$ clearly indicated that the diffusion is the dominant mechanism of drug release from these formulations. Diffusion is related to transport of drug from the dosage matrix into the in vitro study fluid depending on the concentration of the hydrophilic polymer. As gradient varies, the drug is released, and the distance for diffusion increases. This could explain why the drug diffuses at a comparatively slower rate as the distance for diffusion increases.

4. Conclusion

All the pre-compression and post compression parameters of the developed formulations of fentanyl citrate matrices were practically within control limits. Sustained release matrix tablets of this opioid were prepared by wet granulation technique using CCD, where the effect of independent variables, HPMCK 15M and Ethyl cellulose on dependent response variables such as percent drug released at 2, 12 and 24 h were considered to get an optimized formulation for once a day administration and the selection for it was made on the basis of $T_{50\%}$. Formulation M9 showed 50% drug release in 12 h which was considered a formulation suitable for once a day administration. Formulation M9 gave “n” values less than 0.5, which indicated the non-Fickian release i.e. initially there is rapid release, which is followed by tailing off overtime. The dissolution profile was found to be of matrix type. The factorial study indicates a good correlation coefficient (0.987–0.999). Controlled drug release following Higuchi kinetics attained in the current study indicated that the hydrophilic matrix tablets of drug, prepared using HPMCK 15M and ethyl cellulose N10 can successfully be employed as once-a-day oral controlled release drug delivery system. Higher amount of polymers decreased rate and extent of drug release. Release rate of the drug from the matrix tablets was significantly influenced by the concentration of HPMCK 15M compared to the effect of concentration of EC N10 at 2 and 12 h,

| Trial No. | $N$   | $K_H$ | $R^2$ |
|-----------|-------|-------|-------|
| M1        | 0.4898| 31.21 | 0.992 |
| M2        | 0.5022| 32.23 | 0.993 |
| M3        | 0.5113| 31.11 | 0.994 |
| M4        | 0.5154| 32.18 | 0.993 |
| M5        | 0.5465| 33.23 | 0.997 |
| M6        | 0.5187| 29.98 | 0.991 |
| M7        | 0.5799| 34.24 | 0.990 |
| M8        | 0.5312| 30.11 | 0.987 |
| M9        | 0.5099| 24.56 | 0.999 |
| M10       | 0.5863| 33.78 | 0.998 |
| M11       | 0.5532| 32.17 | 0.999 |
| M12       | 0.5823| 33.87 | 0.998 |
| M13       | 0.5998| 34.23 | 0.999 |
Figure 3, whereas release rate of the drug from the matrix tablets was significantly influenced by the concentration of EC N10 than concentration of HPMCK 15M at 24 h, Figure 4.

This indicates both the polymers play an important role for the sustained release of opioid drug. However, appropriate balancing between various levels of the two polymers may contribute better results. High degree of prognosis obtained using RSM corroborates that a 2-factor CCD is quite efficient in optimizing drug delivery systems that exhibit nonlinearity in response(s).

Results of the present study, altogether demonstrated that combination of both hydrophilic and hydrophobic polymers could be successfully employed for formulating sustained-release matrix tablets of fentanyl citrate. The investigated sustained release formulations of the drug are capable maintaining constant plasma drug concentration through 24 h. However extensive in vitro in vivo correlation studies on similar formulations are essential to establish a successful formulation from the biopharmaceutical view point.

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