**Central Composite Design Assisted Formulation Development and Optimization of Gastro-retentive Floating Tablets of Polyherbal**

###### ABSTRACT

**Objectives: The present f**ormulation contains a blend of natural ingredients such as *Glycyrrhiza glabra* (Liquorice), *Syzygium aromaticum* (Clove)*, Curcuma longa* (Turmeric) and *Ocimum sanctum* (Tulsi).The existing study is concerned with the formulation and optimization of polyherbal floating tablets via central composite design. **Materials and Methods:** Direct compression method was employed to prepare the tablets. Drug -excipient studies were executed through FT-IR and DSC analysis. The independent variables selected were the concentrations of HPMC K4M (X1 ) and Ethyl cellulose (X2 ). The dependent variables designated were Floating Lag Time (FLT) and Drug Release (DR) at 10 hrs. The model was found to be nonlinear and the curvature effect was significant. Hence, the system suggested to central composite design. **Results:** FT-IR studies demonstrated that there is no considerable interaction amid the drug and the excipients. Also, studies revealed that drug and excipient were compatible as there is no significant alteration in melting point of drug when blended with excipients. The precompression parameters of the formulations showed good flow properties. The evaluation of post compression parameters indicated that all the prepared formulations were within the specified limits. Floating lag time of formulations (F1-F9) were found to be less than 1 min and total floating time exceeding 8 hrs. Percentage cumulative drug release of all formulations (F1-F9) were in the range of 65% to 95%. The obtained design space/contour plots were used for selecting batches in desirable ranges. **Conclusion:** The results revealed that experimental design was successfully used to optimize polymer concentrations. It was determined that the central composite design would be used to formulate polyherbal gastro-retentive floating tablets with fewer trials and higher quality features.

**Key words:** Gastroretentive floating tablet, *Glycyrrhiza glabra*, *Syzygium aromaticum, Curcuma longa*, *Ocimum sanctum,* HPMC K4M, Ethyl cellulose

**INTRODUCTION**

The Gastrointestinal tract is essentially a tube about nine meters long that runs through the middle of the body from the mouth to the anus and includes the throat, esophagus, stomach, small intestine and large intestine. The stomach is an organ with a capacity for storage and mixing (Cultrone A. et al., 2015). The antrum region is responsible for the mixing and grinding of gastric contents. Under fasting conditions, the stomach is a collapsed bag with a residual volume of approximately 50ml and contains a small amount of gastric fluid (pH 1–3) and air (Singh, L et al., 2011). The GI tract is in a state of continuous motility consisting of two modes, inter-digestive motility pattern and digestive motility pattern. The former is dominant in the fasted state with a primary function of cleaning up the residual content of the upper GI tract (Browning, K. N. et al., 2019). The inter-digestive motility pattern is commonly called the ‘migrating motor complex’ (‘MMC’) and is organized in cycles of activity and quiescence. The stomach is j shaped organ located in the upper left hand portion of the abdomen just below the diaphragm. It occupies a portion of the epigastric and left hydro-chondral region. Due to its small surface area, very little absorption takes place from the stomach. Cardia, Fundus, Body and Pylorus are the four regions of stomach (Takahashi, T. et al., 2013). Various factors like the absorption ability, pre-systemic clearance, gastric motility, and gastrointestinal emptying time will have an influence on the bioavailability of drug from the dosage form. Both neural and hormonal mechanisms control the secretion of gastric juice and the contraction of smooth muscles in the stomach wall (Vinarov, Z. et al., 2021; Rangaraj, N et al., 2022). Events in gastric secretion occur in three overlapping phases: cephalic phase, gastric phase and intestinal phase. Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 states. During the fasting state an inter-digestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours. This is called the inter-digestive Myelomeningocele or migrating motor complex (MMC), which is further divided into following 4 phases as described by Wilson and Washington (Goyal, R. K. et al., 2019).[7]

Stomach acts as reservoir for holding food, control rate at which food enters to duodenum and secrete gastric juice, which contains hydrochloric acid, pepsin, intrinsic factor and gastric lipase. Also, it helps in grinding, fluidization and primary digestion of stomach contents and mixes food and gastric juice to form chyme (Sensoy, I. et al., 2021). Floating i.e. Low density form of the dosage form that buoyant in gastric fluid, high density dosage form that us retained in the bottom of stomach, bio-adhesion to stomach mucosa and expansion by swelling or unfolding to a large size which limits emptying of the system through the pyloric sphincter are the several techniques of GRDDS (Tripathi, J. et al., 2019). Based on the buoyancy mechanism, floating systems are classified as Non-Effervescent systems and Effervescent systems. Effervescent system includes use of gas generating agent carbonates (e.g. citric acid and tartaric acid) present in the formulation to produce carbon dioxide CO2 gas, thus reducing the density of the system and making it float on the gastric fluid. The main mechanism involved in this system is the production of carbon-dioxide (Vinchurkar, K et al..). These systems are further classified as Volatile liquid containing systems and Gas generating systems (Janhavi, Z. S, et al, 2015)

Curcumin is the primary active compound derived from the rhizome of the turmeric plant. It is known for its vibrant yellow color and has been used in traditional medicine for centuries (Sharifi-Rad, J. et al., 2020).

Liquorice is a perennial herb known for its sweet-tasting root. Glycyrrhizin ((also known as glycyrrhizic acid or glycyrrhizinic acid) are the active constituents of Liquorice. Flavonoids are the active constituents ofLiquorice which has been used in traditional medicine for its therapeutic properties (Pastorino, G. et al., 2018 ; Wahab, S. et al., 2021). Clove is a spice derived from the flower buds of the clove tree. It contains eugenol and flavonoids known for its strong aroma and flavor. Also, it is effective against various pathogens, including H. pylori (Cortés-Rojas et al., 2014). Tulsi is a sacred herb in Ayurvedic medicine, renowned for its medicinal properties and aromatic leaves. It contains eugenol and flavonoids which exhibits antibacterial effects against H. pylori (Dwivedi Pradeep et al., 2023).

**MATERIALS AND METHODS OF PREPARATION OF HERBAL FLOATING TABLETS:**

To investigate the properties of hair care, various plant parts were chosen. The plants are *Glycyrrhiza glabra* (Liquorice), *Syzygium aromaticum* (Clove)*, Curcuma longa* (Turmeric) and *Ocimum sanctum* (Tulsi). All of the necessary powders for these unrefined medications were gathered from the market of the nearby herbal pharmacy. After being precisely weighed, these powders were run through sieve number 100. It was then combined with constant trituration and kept in sealed jars (Sahoo, S.et al., 2024; Bhardwaj, P. et al. 2010).

**FT-IR studies**

The drug's compatibility with the excipients was determined using FT-IR spectroscopy. Small quantities of the medication and polymers are combined with KBr and squeezed to produce tiny pellets. These are analysed with FT-IR spectrophotometer and scanned in 4000 cm-1 to 400 cm-1 range (Krishnaiah, Y. S. R et al., 2003).

**Optimization by the CCD**

Central composite design technique was used to formulate a design, total 9 experimental formulation of HPMC K4M and Ethyl cellulose floating tablets containing Polyherbal drugs were prepared. Present investigation was performed by taking two variable factors HPMCK4M (X1) and Ethyl cellulose (X2). The two responses were selected Floating Lag time (Y1) and % CDR (F2). Overview of the experimental plan and observed response values were found by CCD. The outcome of model analysis like sum of squares, mean square, F – value, P – values were found from ANOVA. Contour plot and 3D surface plot were studied by design of experiment software– version 13 (Hassan, H. et al., 2021).

**Preparation of Polyherbal floating tablets**

Polyherbal floating tablets were prepared by direct compression utilising varied ratios of HPMC K4M and Ethyl cellulose. Sodium bicarbonate was used as a gas producing agent. Each ingredient was precisely weighed and screened via sieve 40. All the ingredients were combined homogeneously in a glass mortar. Later on, magnesium stearate was mixed. Table 3 shows the composition of several formulations. Hardik Engineering, India was used to compress the resultant mass (Yehualaw A. et al. 2023).

#### Phytochemical Tests for Clove, Curcumin, Liquorice, and Tulsi

Pharmacognosy involves the study of medicinal drugs derived from plants and other natural sources. The following tests can be conducted on clove, curcumin, liquorice, and tulsi to analyze their pharmacognostic properties (Adebisi, A. A. et al., 2021; Ogwuda, U. A. et al., 2022 ; Grover, M. et al., 2021).

**Clove (Syzygium aromaticum)**

**Microscopic Examination:**

Transverse Section: The presence of oil cells, tracheid, and fibers were identified with the help of microscope.

**Physicochemical Analysis:**

**Moisture Content:** Determine moisture content using the drying method.

**Ash Value:** Conduct total ash, acid-insoluble ash, and water-soluble ash tests to assess purity.

**Chemical Tests:**

Eugenol Test: Add a drop of dilute hydrochloric acid to clove powder. A pink color indicates the presence of eugenol.

**Curcumin (Curcuma longa)**

**Microscopic Examination:**

**Powder Microscopy:** Observe the powdered form under a microscope to identify starch grains, fibers, and other cellular structures.

**Physicochemical Analysis:**

**Solubility Test:** Test solubility in water, ethanol, and chloroform to determine its extraction properties.

**Chemical Tests:**

**Curcumin Test:** Add sodium hydroxide to curcumin dissolved in ethanol. A deep yellow color indicates the presence of curcumin.

**Liquorice (*Glycyrrhiza glabra*)**

**Microscopic Examination:**

**Transverse Section**: Examine the root under a microscope to identify the presence of lignified fibers, parenchyma, and starch grains.

**Physicochemical Analysis:**

**Moisture Content**: Assess moisture content using drying methods.

**Ash Value**: Measure total ash, acid-insoluble ash, and water-soluble ash values.

**Chemical Tests:**

**Glycyrrhizin Test**: Dissolve liquorice powder in water, filter, and add hydrochloric acid. The formation of a yellow color indicates the presence of glycyrrhizin.

**Tulsi (*Ocimum sanctum*)**

**Microscopic Examination:**

**Powder Microscopy:** Examine the powdered form of Tulsi leaves for the presence of epidermal cells, stomata, and glandular trichomes.

**Physicochemical Analysis:**

**Moisture Content:** Determine moisture content using standard drying methods.

**Ash Value:** Conduct total ash and acid-insoluble ash tests for purity assessment.

**Chemical Tests:**

**Essential Oil Test:** Steam distill the leaves and analyze the essential oil content. Test for the presence of eugenol and other compounds.

**Pre compression Parameters** (Youssef N.A. et al.,2015; Balaji Maddiboyina et al., 2020)

***Bulk Density (BD)***

The BD was determined by placing a weighed sample in a 100 mL graduating cylinder. The preliminary volume and mass are recorded and calculated the BD.9

***Tapped Density (TD)***

It is valued by using TD apparatus (Electrolab ETD-1020, India)

utilizing the total mass and tapped volume employing a graduated

cylinder, subjected for 100 tappings.10

***Angle of Repose (AR)***

It is the highest feasible slant amid the powder pile surface and

the horizontal plane,11 and is valued by tan Ɵ = h/r

θ = tan-1(h/r)

where,

θ = angle of repose

h = height of pile

r = radius of the base of the pile

***Carr’s index (CI)***

**CI was estimated determined by considering TD and BD.12**



**Hausner ratio:** Hausners ratio is an index of ease of powder flow; it is calculated by the following formula.

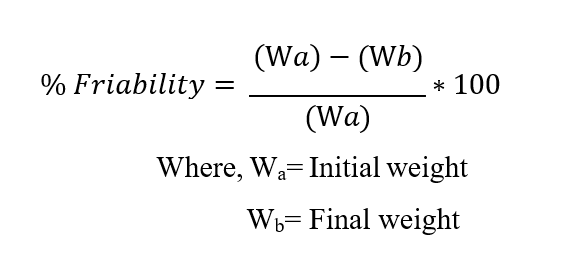


**Post-compression parameters** (Mohapatra, P. K. et al., 2020 ; Singh R. et al., 2023)

**Tablet thickness and Diamete**r: Thickness and diameter of tablets were important for uniformity of tablet size. Thickness and diameter were measured using Vernier calipers.

**Hardness:** This test used to check the hardness of a tablet which may undergo chipping or breakage during storage, transportation and handling. In this five tablets will select at random and the hardness of each tablet will measure with Pfizer hardness tester. The hardness is usually measured in terms of kg/cm2.

**% Friability:** The friability test was carried out in Roche friabilator to evaluate the hardness and stability instantly. Twenty tablets weighed (Wa) initially and put in a tumbling and rotating apparatus drum. Then, they are subjected to fall from 6 inches height. After completion of 100 rotations, the tablets again weighed (Wb). The percent loss in weight or friability (f) calculated by the formula given below:

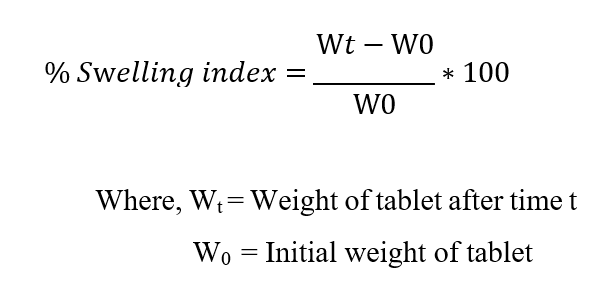


**Uniformity of weight:** This test is performed to maintain the uniformity of weight of each tablet which should be in the prescribed range, this is done by sampling and weighing 20 tablets at random and average weight is calculated. Not more than two of the individual weights deviate from the average weight by more than the percentage and none deviate by more than twice the percentage. Weight variation specification as per I.P is shown in table.

**Floating Lag Time:** The time taken by the tablet to emerge onto the surface of dissolution medium, at pH 1.2, temperature 37±0.5°C, paddle rotation at 50 rpm and 900ml as volume, it is measured using stopwatch.

**Total Floating Time:** The time taken by the tablet to float constantly on the surface of the dissolution fluid, at pH 1.2, temperature 37±0.5°C, paddle rotation at 50 rpm it is measured using stopwatch.

**% Swelling study:** The swelling of the polymers can be measured by their ability to absorb water and swell. The swelling property of the formulation can be determined by various techniques. The swelling study can be done by using USP dissolution apparatus II. Distilled water can be used as medium, 900 ml rotated at 50 rpm. The temperature of medium should be maintained at 37±0.5 ◦C throughout the study. After a selected time intervals, the tablets should be withdrawn, blotted to remove excess water and weighed. Swelling characteristics can be expressed as below formula,



***In vitro* Drug Release**

To assess the drug release of Polyherbal floating tablets (basket type) was used. At 37.5°C and 50 rpm, 900 mL of 0.1N HCl was used as dissolving medium. Hourly for 8 hrs, a sample (5 mL) of the aliquot was removed, filtered and substituted with media.22 Shimadzu UV-1700 was availed to measure the absorbance of these solutions at 278 nm.

**Table 1: Coded variables with responses**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Factors | **Actual values (mg)** | | | | | Responses |
|  | -2 | -1 | 0- | +1 | +2 |  |
| HPMCK4M (X1) | 50 | 60 | 70 | 80 | 90 | Floating lag time |
| Ethyl cellulose (X2) | 30 | 45 | 60 | 75 | 90 | % CDR |

**Table 2: Investigational strategy layout.**

|  |  |  |
| --- | --- | --- |
|  | **Formulation code** | **Combinations** |
| Factorial Design  Mid-point  Central Composite Design | F1 | I |
| F2 | X1 |
| F3 | X2 |
| F4 | X1X2 |
| F5 | Mid-point |
| F6 | X1 at -2L |
| F7 | X1 at+2L |
| F8 | X2 at -2L |
| F9 | X2 at +2L |

**Table 3: Composition of Polyherbal floating tablets (F1 – F9).**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ingredient** | **F1** | **F2** | **F3** | **F4** | **F5** | **F6** | **F7** | **F8** | **F9** |
| Liquorice (mg) | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| Clove (mg) | 75 | 75 | 75 | 75 | 75 | 75 | 75 | 75 | 75 |
| Curcumin (mg) | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 |
| Tulsi(mg) | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 |
| Sodium bicarbonate (mg) | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 |
| HPMC K4M (mg) | 60 | 80 | 60 | 80 | 55.85 | 84.15 | 70 | 70 | 70 |
| Ethyl cellulose (mg) | 45 | 45 | 75 | 75 | 60 | 60 | 38.79 | 81.21 | 60 |
| MCC PH 102 (mg) | 100 | 80 | 70 | 50 | 89.15 | 60.85 | 96.21 | 53.79 | 75 |
| Magnesium stearate (mg) | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Total weight (mg) | 470 | 470 | 470 | 470 | 470 | 470 | 470 | 470 | 470 |

**RESULTS**

**Phytochemical Tests:**

The phytochemical tests for active ingredients like clove, curcumin (turmeric), tulsi (holy basil), and liquorice (liquorice) with their corresponding properties such as alkaloid, flavonoid, tannin, glycoside, saponins, and steroid presence:

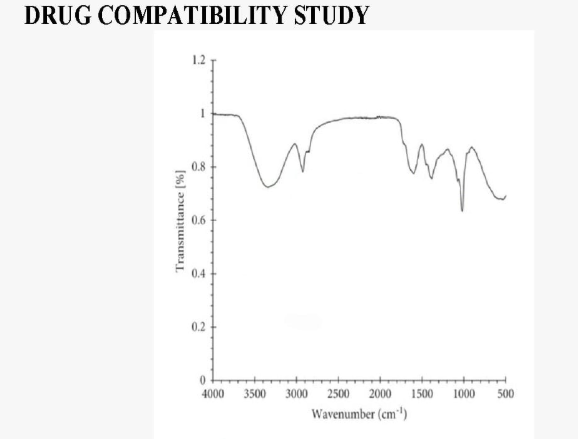
List 1 : **The table shows the phytochemical tests for active ingredients**

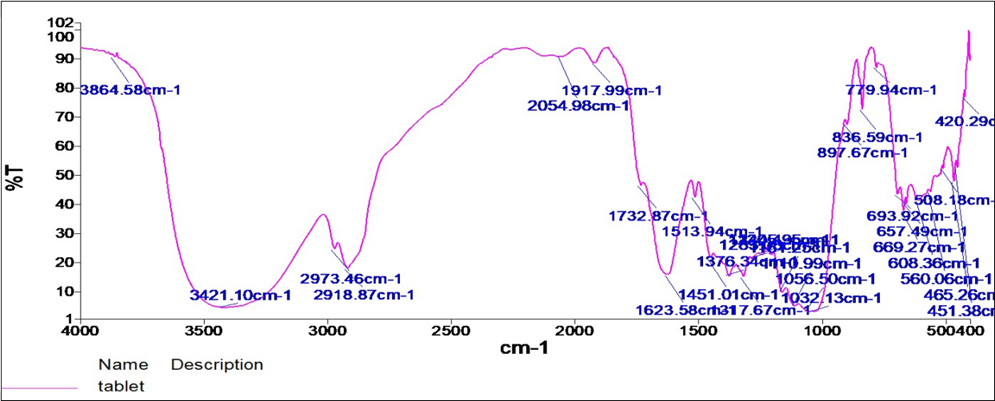
|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Phytochemical Test** | **Clove** | **Curcumin (Turmeric)** | **Tulsi (Holy Basil)** | **Liquorice** |
| **Alkaloids** | + | - | + | + |
| **Flavonoids** | + | + | + | - |
| **Tannins** | + | - | + | + |
| **Glycosides** | - | + | + | + |
| **Saponins** | - | - | + | + |
| **Steroids** | - | - | - | + |

**FT-IR studies** :

According to FT-IR investigations on drug excipients compatibility test, it was found that there are no alterations in the spectra of the drug and excipients used. The results were represented in Figures 1 and 2 respectively.

Picture 1 : Drug Compatibility study





**Table 4: INTERPRETATION** (Pavia, D. et al., 2001)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **No.** | **WAVE NUMBER RANGE (cm-1)** | **WAVE NUMBER(cm-1)** | **WAVE NUMBER (cm-1)** | **FUNCTIONAL GROUP** |
| 1 | 3700-4000 | - | 3864.58 | N-H,O-H |
| 2 | 3200-3600 | 3280.54 | 3421.10 | Phenolic (O-H) |
| 3 | 2850-2950 | 2918.34 | 2918.87 | Aliphatic (C-H) |
| 4 | 1800-2000 | - | 1917.99 | Anhydrides and acid chloride |
| 5 | 1700-1750 | 1736.10 | 1732.87 | Saturated ketones/ esters (C=O) |
| 6 | 1600-1680 | 1635.20 | 1623.58 | Aryl ketone (C=O) |
| 7 | 1500-1520 | - | 1513.94 | Aromatic/carbonyl(C=C/C=O) |
| 8 | 1400-1450 | 1462.39 | 1451.01 | Aromatic ring (C=C) |
| 9 | 1200-1270 | 1254.88 | 1263.81 | Aryl ether (C-O) |
| 10 | 1100-1180 | - | 1110.99 | Ketone (C-CO-C) |

**Pre compression Parameters**

**Table 5: Precompression parameters of F1-F9 formulations**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Formulation** | **Bulk Density ± SD** | **Tapped Density ± SD** | **Angle of repose ± SD** | **Hausner ratio ± SD** | **Carr’s Index ± SD** |
| **F1** | 0.632±0.002 | 0.745±0.026 | 32±0.83 | 1.17±0.040 | 15.16±0.098 |
| **F2** | 0.504±0.003 | 0.619±0.040 | 34±0.33 | 1.22±0.010 | 18.57±0.871 |
| **F3** | 0.412±0.005 | 0.521±0.046 | 35±0.16 | 1.07±0.025 | 20.92±0.545 |
| **F4** | 0.312±0.021 | 0.422±0.043 | 39±0.16 | 1.02±0.094 | 26.06±0.977 |
| **F5** | 0.424±0.010 | 0.514±0.048 | 37±0.50 | 1.11±0.029 | 15.87±0.697 |
| **F6** | 0.454±0.002 | 0.553±0.026 | 35±0.16 | 1.21±0.044 | 17.90±0.150 |
| **F7** | 0.552±0.009 | 0.655±0.028 | 37±0.33 | 1.18±0.018 | 17.79±0.074 |
| **F8** | 0.406±0.012 | 0.512±0.029 | 39±0.16 | 1.26±0.079 | 20.70±0.092 |
| **F9** | 0.456±0.001 | 0.556±0.029 | 34±0.50 | 1.21±0.040 | 17.98±0.024 |

**n=3 Entire values are stated as mean±SD**

**Table 6: Post compression parameters of F1-F9 formulations**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Formulation** | **Thickness ± SD (mm)** | **Hardness ± SD (kg/cm2)** | **% Friability ± SD** | **Floating lag time (sec)** | **Total floating time (hrs)** |
| **F1** | 4.2±0.33 | 6.2±0.03 | 0.62±0.003 | 28±0.16 | >8 |
| **F2** | 4.1±0.01 | 6.8±0.03 | 0.68±0.003 | 35±0.50 | >8 |
| **F3** | 4.2±0.05 | 6.7±0.01 | 0.67±0.001 | 51±0.33 | >8 |
| **F4** | 4±0.03 | 7.1±0.05 | 0.71±0.005 | 54±0.33 | >8 |
| **F5** | 4.2±0.01 | 7.0±0.01 | 0.70±0.003 | 25±0.50 | >8 |
| **F6** | 4.2±0.03 | 7.3±0.03 | 0.73±0.003 | 29±0.83 | >8 |
| **F7** | 4.3±0.01 | 6.3±0.03 | 0.63±0.003 | 21±0.66 | >8 |
| **F8** | 4.2±0.01 | 7.8±0.01 | 0.78±0.005 | 52±0.16 | >8 |
| **F9** | 4.1±0.01 | 7.2±0.03 | 0.72±0.003 | 46±0.16 | >8 |

**Table 7: Statistical analysis of DOE experimental observations of Y1 (Floating lag time)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| S.No. | **Combination** | **Name of variable** | **Coefficient values** | **SS % (% of**  **sum of squares)** |
| 1 | b0 | - | 36.0 | 895.88 |
| 2 | b1 | HPMC K4M | -3.64 | 106.16 |
| 3 | b2 | Ethyl cellulose | 8.19 | 536.72 |
| 4 | b1 b2 | HPMC K4M + Ethyl cellulose | -0.75 | 2.25 |

**Table 8: Results of ANOVA for response Y1 (floating lag time)**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **S.No.** | **Source of**  **variable** | **SS** | **DF** | **MS** | **F-value** | **p-value** |
| 1 | Model | 895.88 | 5 | 179.18 | 4480.60 | < 0.0001 |
| 2 | Residual | 0.1200 | 3 | 0.0400 | - | - |
| 3 | Total | 896.00 | 8 | - | - | - |

\*SS is Sum of squares, MS is Mean squares, DF is Degree of freedom

|  |  |
| --- | --- |
|  |  |
| **Fig. 1a: Contour plot showing effect of HPMC K4M (X1) and Ethyl cellulose (X2) on Floating Lag Time (Y1)** | **Fig. 1b: 3D showing effect of HPMC K4M (X1) and Ethyl cellulose (X2) on Floating Lag Time (Y1)** |

**Floating lag time (Y1)**

X1 showed more effect in FLT (Y1) as compared to X2 as indicated in Table 7.

**Final Equation in Terms of Coded Factors**

**Y1 =** 36.0 -3.64 X1 + 8.19 X2 -0.75 X1X2 -7.00 X12 + 0.25 X22

**Final Equation in Terms of Actual Factors**

**Y1 =** 36.0 -3.64 HPMCK4MX1 + +8.19 Ethyl cellulose X2 -0.7500 HPMCK4M Ethyl cellulose X1X2 -7.00 HPMCK4M X12 + 0.25 Ethyl cellulose X22

A polynomial equation predicts the outcome of independent variables at unlike levels on response variables. Multinomial calculations were used to make a conclusion after analysing the amount of the co-efficient and the mathematical signs it possesses. The Model F-value of 4480.60 implies the model was significant as shown in table 8. The obtained *F* value found to be 4480.60 which is bigger than the tabulated value. In this case, the P-values obtained was less than 0.0500 which indicates the model terms was significant. Also, X1, X2, X1X2 and X12 are significant model terms. R2 values Floating Lag Time (FLT) was found to be 0.9997 which indicates good correlation between dependent and independent variables. As a result, the connection between Y1 and X1 X2 was non-linear, as indicated by software and the CCD remains in place. Multiple Linear Regression (MLR) study revealed that lowering the concentration of Ethyl cellulose (X2) retards the FLT. The FLT and TFT were found to be less than 1 min. and it float more than 8 hrs respectively. Also, gas generating agent sodium bicarbonate was used which supports the tablet to float on the surface of media. From the results of multiple regression analysis, it was found that Ethyl cellulose (X2) factors had statistically significant influence on Y1 (Floating Lag Time) dependent variables as p <0.05. Data were analyzed using Design of Expert version 13.

**Table 9: Statistical analysis of DOE experimental observations of Y2 (% CDR)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| S.No. | **Combination** | **Name of variable** | **Coefficient values** | **SS % (% of**  **sum of squares)** |
| 1 | b0 | - | +79.00 | 727.15 |
| 2 | b1 | HPMC K4M | +2.29 | 41.92 |
| 3 | b2 | Ethyl cellulose | -8.19 | 536.72 |
| 4 | b1 b2 | HPMC K4M + Ethyl cellulose | -2.75 | 30.25 |

**Table 10: Results of ANOVA for response Y2 (% CDR)**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **S.No.** | **Source of**  **variable** | **SS** | **DF** | **MS** | **F-value** | **p-value** |
| 1 | Model | 727.15 | 5 | 145.43 | 152.87 | 0.0008 |
| 2 | Residual | 2.85 | 3 | 0.9513 | - | - |
| 3 | Total | 730.00 | 8 | - | - | - |

\*SS is Sum of squares, MS is Mean squares, DF is Degree of freedom

|  |  |
| --- | --- |
|  |  |
| **Fig. 2a: Contour plot showing effect of HPMC K4M (X1) and Ethyl cellulose (X2) on %CDR (Y2)** | **Fig. 2b: 3D showing effect of HPMC K4M (X1) and Ethyl cellulose (X2) on %CDR (Y2)** |

**% Cumulative drug release (Y2)**

Both X1 and X2 give effect on %CDR as indicated in Table 9.

**Final Equation in Terms of Coded Factors**

**Y2 =** 79.0 + 2.29 X1 -8.19 X2 -2.75 X1X2 + 4.12 X12 – 1.12 X22

**Final Equation in Terms of Actual Factors**

**Y2 =** 79.0 + 2.29 HPMC K4M X1 - 8.19 Ethyl cellulose X2 -2.75 HPMC K4M Ethyl cellulose X1X2 + 4.12 HPMC K4M X12 – Ethyl cellulose 1.12 X22

A polynomial equation predicts the outcome of independent variables at unlike levels on response variables. Multinomial calculations were used to make a conclusion after analysing the amount of the co-efficient and the mathematical signs it possesses. The Model F-value of 152.87 implies the model was significant as shown in table 10. The obtained *F* value found to be 152.87 which is bigger than the tabulated value. In this case, the P-values obtained was less than 0.0500 which indicates the model terms was significant. Also, X1, X2, X1X2 and X12 are significant model terms. R2 values % CDR was found to be 0.9961 which indicates good correlation between dependent and independent variables. As a result, the connection between Y1 and X1 X2 was non-linear, as indicated by software and the CCD remains in place. Multiple Linear Regression (MLR) study revealed that increasing the concentration of Ethyl cellulose (X2) retards the % CDR. The % CDR were found to be in the range of 65 % to 95 % and it will release drug for 8 hrs. Also, gas generating agent sodium bicarbonate was used which supports the tablet to float on the surface of media. From the results of multiple regression analysis, it was found that Ethyl cellulose (X2) factors had statistically significant influence on Y1 (% CDR) dependent variables as p <0.05. Moreover, higher the concentration of HPMC K4M helps in more releasing polyherbal drugs. Data were analyzed using Design of Expert version 13.

***List 2 : In-vitro* drug release**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Time**  **(in hours)** | **F1** | **F2** | **F3** | **F4** | **F5** | **F6** | **F7** | **F8** | **F9** |
|  |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |  |
| 1 | 13 | 15 | 8 | 12 | 12 | 15 | 13 | 11 | 15 |  |
| 2 | 21 | 23 | 16 | 20 | 19 | 29 | 18 | 19 | 22 |  |
| 3 | 32 | 31 | 25 | 25 | 27 | 39 | 29 | 26 | 33 |  |
| 4 | 41 | 39 | 32 | 36 | 33 | 48 | 37 | 35 | 38 |  |
| 5 | 57 | 47 | 49 | 49 | 44 | 60 | 42 | 49 | 44 |  |
| 6 | 61 | 55 | 56 | 52 | 47 | 71 | 53 | 51 | 56 |  |
| 7 | 75 | 63 | 61 | 64 | 54 | 84 | 70 | 59 | 70 |  |
| 8 | 86 | 91 | 75 | 73 | 83 | 95 | 88 | 65 | 79 |  |

**Validation by Check point batch** (Bolton S. et al., 2007)

To confirm the validity of response surface plot and equation generated by multiple regression analysis, a check point batch was prepared shown in table 11. An overlay plot was obtained by adding desired range of evaluation parameters from Design Expert 14. The overlay plot is shown in Fig. 3. Yellow colour area in overlay plot showed optimum concentration range for desired result. A batch was prepared by taking concentration of HPMC K4M (X1) and Ethyl cellulose (X2) observed in overlay plot and the actual responses were evaluated from the prepared check point batch. The overlay plot indicated that optimum concentration which showed the best result. The practically obtained values were closer to the predicted values as shown in table 11. Thus, it justified the validation of design.

**Table 11: Formulation of Check Point Batch (CPB)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Batch Code | Coded Value | | Actual value | |
| CPB | X1 | X2 | HPMC K4M | Ethyl cellulose |
| 17.02 | 10.77 | 80 | 50.65 |

**Table 12: Results of Check Point Batch ()**

|  |  |  |
| --- | --- | --- |
| Response | Predicted value | Actual value |
| Floating Lag Time (FLT) in sec | 20.82 | 21.12 |
| % CDR | 91.78 | 90.27 |

|  |
| --- |
|  |
| **Fig. 3: Overlay plot of check point batch (CPB)** |

**CONCLUSION:**

Now-a-days people are shifting towards natural therapy due to its no side effects and it is found in abundant. The present investigation utilizes the central composite design to optimize the polyherbal batches. Also, it explores the efficacy of floating tablets of polyherbal formulation for the treatment of gastritis by inhibiting H. pylori.

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