**Formulation Development and Optimisation of Polyherbal Gastro-retentive Floating Tablets Using Central Composite Design**

###### ABSTRACT

**Background:** The stomach is an organ with a capacity for storage and mixing. The Gastrointestinal tract (GI) is in a state of continuous motility, consisting of two modes: the inter-digestive motility pattern and the 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. **Objectives:** The presentformulation 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 optimisation of polyherbal floating tablets via central composite design. **Materials and Methods:** The 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 8 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 between the drug and the excipients. Also, studies revealed that the drug and excipient were compatible, as there is no significant alteration in the melting point of the drug when blended with excipients. The pre-compression 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. The floating lag time of formulations (F1-F9) was found to be less than 1 min, and the total floating time exceeded 8 hrs. The percentage cumulative drug release of all formulations (F1-F9) was 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 optimise 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.

**Keywords:** *Gastroretentive floating tablet, Glycyrrhiza glabra, Syzygium aromaticum, Curcuma longa, Ocimum sanctum, 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, oesophagus, stomach, small intestine and large intestine. The stomach is an organ with a capacity for storage and mixing (Cultrone A. et al., 2015; Pumjan S. et al.,2025). 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). This intricate ecosystem comprises bacteria, archaea, fungi, viruses, and other organisms that coexist with the host in a symbiotic relationship. It is crucial in upholding the equilibrium between wellness and illness within the gastrointestinal system, exerting its influence through myriad physiological functions (Cheemala et al., 2024). The GI tract is in a state of continuous motility consisting of two modes, the inter-digestive motility pattern and the 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 organised in cycles of activity and quiescence. The stomach is a 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 hydrochondral region. A little absorption takes place from the stomach due to its small surface area. Cardia, Fundus, Body and Pylorus are the four regions of the 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 the drug from the dosage form (Nallasamy et al., 2024). 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 takes place, which cycle both through the stomach and the intestine every 2 to 3 hours. This is called the inter-digestive Myelomeningocele or migrating motor complex (MMC), which is further divided into the following 4 phases as described by Wilson and Washington (Goyal, R.K. et al., 2019).

The stomach acts as a reservoir for holding food, controls the rate at which food enters to duodenum and secretes gastric juice, which contains hydrochloric acid, pepsin, intrinsic factor and gastric lipase. Also, it helps in grinding, fluidisation and primary digestion of stomach contents and mixes food and gastric juice to form chyme (Sensoy, I. et al., 2021; Rajora A, et al., 2022). Floating, i.e. Low-density form of the dosage form that is buoyant in gastric fluid, a high-density dosage form that is retained in the bottom of the stomach, bio-adhesion to the stomach mucosa, and expansion by swelling or unfolding to a large size, which limits emptying of the system through the pyloric sphincter are 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. The effervescent system includes the 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)

Entire herb or plant parts have been used since ancient days for the treatment of human ailments and continue to pave the new means of therapeutics at the global level. With the progression in the extraction technology, it is possible to extract and isolate the important bioactive constituents such as glycosides, alkaloids, tannins, steroids, volatile oils, fixed oils, phenols, flavonoids, and resins present in the various portions of the plants. This has made it possible to increase the use of drugs of natural origin, which have been the mainstay in the treatment in recent years (Gupta et al., 2024). Curcumin is the primary active compound derived from the rhizome of the turmeric plant. It is known for its vibrant yellow colour 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 constituent of Liquorice. Flavonoids are the active constituents of Liquorice, 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 their strong aroma and flavour. Also, it is effective against various pathogens, including *H. pylori* (Cortés-Rojas et al., 2014). Tulsi is an accredited herb in Ayurvedic medicine, renowned for its medicinal properties and aromatic leaves. It contains eugenol and flavonoids, which exhibit 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 an FT-IR spectrophotometer and scanned in the 4000 cm-1 to 400 cm-1 range (Krishnaiah, Y. S. R et al., 2003).

**Optimisation by the CCD**

The central composite design technique was used to formulate a design; a total of 9 experimental formulations of HPMCK4M and Ethyl cellulose floating tablets containing Polyherbal drugs were prepared. The 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). An overview of the experimental plan and observed response values was found by CCD. The outcome of model analysis, like the sum of squares, mean square, F-value, and P-values, was 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 3shows 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 analyse 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, tracheids, and fibres was identified with the help of a 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, fibres, 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 the curcumin dissolved in ethanol. A deep yellow colour indicates the presence of curcumin.

**Liquorice (*Glycyrrhiza glabra*)**

**Microscopic Examination:**

**Transverse Section**: Examine the root under a microscope to identify the presence of lignified fibres, 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 colour indicates the presence of glycyrrhizin.

**Tulsi (*Ocimumsanctum*)**

**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 distil the leaves and analyse 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 graduated cylinder. The preliminary volume and mass are recorded and the BD.

***Tapped Density (TD)***

It is valued by using the TD apparatus (Electrolab ETD-1020, India), utilising the total mass and tapped volume employing a graduated cylinder, subjected to 100 tappings.

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

It is the highest feasible slant amid the powder pile surface and the horizontal plane 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:** Hausner's ratio is an index of ease of powder flow; it is calculated by the following formula.

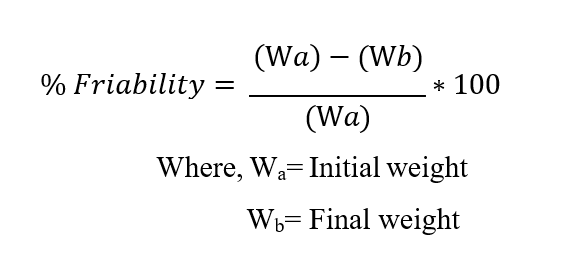


**Post-compression parameters** (Mohapatra, P. K. et al., 2020; Singh R. et al., 2023)

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

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

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

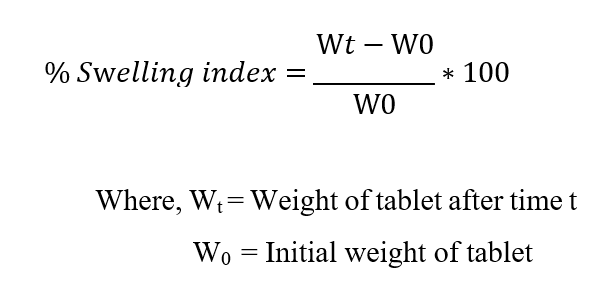


**Uniformity of weight:** This test is performed to maintain the uniformity of weight of each tablet, which should be in the prescribed range. This is done by sampling and weighing 20 tablets at random and average weight is calculated. Not more than two of the individual weights deviate from the average 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 the 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, is measured using a 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 a 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 the USP dissolution apparatus II. Distilled water can be used as a medium, 900 ml, rotated at 50rpm.The temperature of the medium should be maintained at 37±0.5 °C throughout the study. After a selected time interval, the tablets should be withdrawn, blotted to remove excess water and weighed. Swelling characteristics can be expressed as below the formula,



***In vitro* Drug Release**

To assess the drug release of Polyherbal floating tablets, a basket type was used. At 37.5°C and 50 rpm, 900 mL of 0.1N HCl was used as the 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 used 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 |
| HPMCK4M (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 |
| Magnesiumstearate (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:

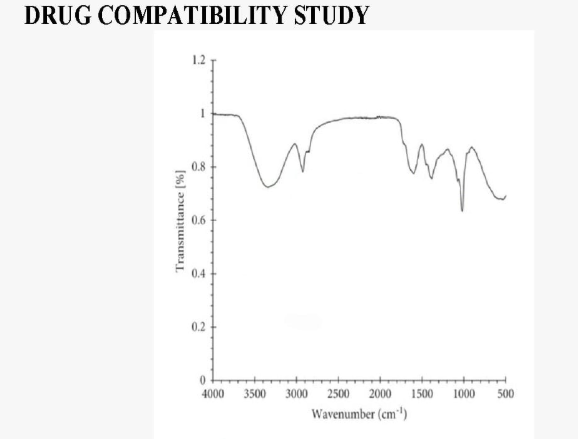
**List 1: The list shows the phytochemical tests for active ingredients**

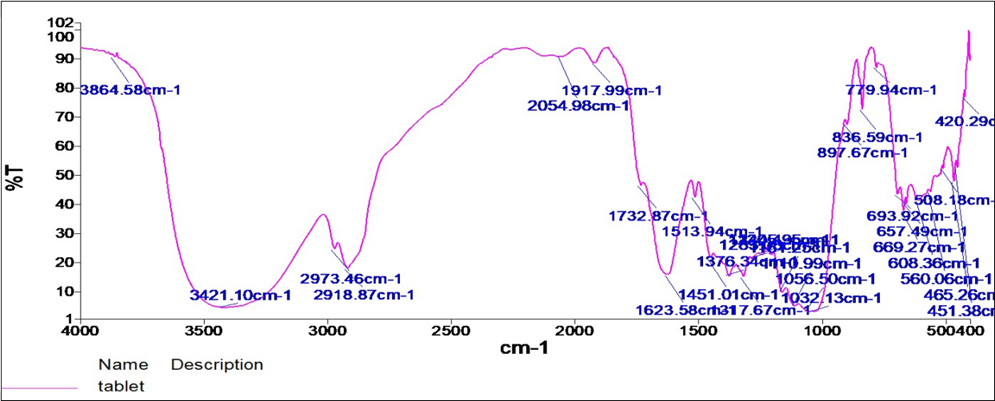
|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Phytochemical Test** | **Clove** | **Curcumin (Turmeric)** | **Tulsi (Holy Basil)** | **Liquorice** |
| **Alkaloids** | + | - | + | + |
| **Flavonoids** | + | + | + | - |
| **Tannins** | + | - | + | + |
| **Glycosides** | - | + | + | + |
| **Saponins** | - | - | + | + |
| **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 the Sum of squares, MS is the Mean squares, and DF is the 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 conclude after analysing the amount of the coefficient 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 was found to be 4480.60which is bigger than the tabulated value. In this case, the P-values obtained were less than 0.0500, which indicates the model terms were 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 the 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 floats for more than 8 hrs respectively. Also, gas-generating agent sodium bicarbonate was used, which supports the tablet to float on the surface of the media. From the results of multiple regression analysis, it was found that Ethyl cellulose (X2) factors had a statistically significant influence on Y1 (Floating Lag Time) dependent variables, as p <0.05. Data were analysed 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 have an 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 was found to be 152.87, which is bigger than the tabulated value. In this case, the P-values obtained were 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 the 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 the drug for 8 hrs. Also, gas-generating agent sodium bicarbonate was used, which supports the tablet to float on the surface of the media. From the results of multiple regression analysis, it was found that Ethyl cellulose (X2) factors had a statistically significant influence on Y1 (% CDR) dependent variables, as p <0.05. Moreover, the higher the concentration of HPMC K4M helps in releasing polyherbal drugs. Data were analysed 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 the response surface plot and equation generated by multiple regression analysis, a checkpoint batch was prepared shown in Table 11. An overlay plot was obtained by adding the desired range of evaluation parameters from Design Expert 14. The overlay plot is shown in Fig. 3. The Yellow colour area in the overlay plot showed the optimum concentration range for the desired result. A batch was prepared by taking the concentration of HPMC K4M (X1) and Ethyl cellulose (X2) observed in the overlay plot, and the actual responses were evaluated from the prepared checkpoint batch. The overlay plot indicated the 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 the 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 (CPB)**

|  |  |  |
| --- | --- | --- |
| 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 checkpoint batch (CPB)** |

**CONCLUSION:**

Nowadays, people are shifting towards natural therapy due to its no side effects and it is found in abundance. The present investigation utilises the central composite design to optimise the polyherbal batches. Also, it explores the efficacy of floating tablets of polyherbal formulation for the treatment of gastritis by inhibiting *H. pylori*.

**DISCLAIMER (ARTIFICIAL INTELLIGENCE)**

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

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