FORMULATION AND CHARACTERIZATION OF FLOATING TABLET DOSAGE FORM OF DUAL DELIVERY OF DRUG CURCUMIN AND BERBERINE HYDROCHLORIDE USING SIMULTANEOUS ESTIMATION BY UV SPECTROSCOPY

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ABSTRACT

Objective: The present study was aimed to develop a combinational floating tablet of curcumin and berberine HCl utilizing synthetic polymers HPMC K-100M, HPMC K-15M, and F127. The formulations were developed by the process of wet granulation and evaluated for drug content, content uniformity, floating lag time, total floating time, in vitro buoyancy studies, and in vitro drug release profile. A simultaneous estimation method for curcumin and berberine was developed using UV spectrophotometry.

Methods: The formulations were developed by the process of wet granulation and evaluated for drug content, content uniformity, floating lag time, total floating time, in vitro buoyancy studies, and in vitro drug release profile. A simultaneous estimation method for curcumin and berberine was developed using UV spectrophotometry.

Results: The results clearly indicated that the tablets produced were having acceptable physical parameters. The absence of any drug/polymer/excipient interactions was confirmed using infrared spectroscopy. It was found that the drug content of was in between 96.22 to 99.45 % in all the formulations. Because of their low densities, the floating test showed good results. The formulations could float for more than 8 h. The in vitro release studies confirmed the sustained release of more than 80 percent of drug contained within a period of 8 h. In vitro buoyancy was confirmed in all three batches (F1-F3). The overall floating time for the F2 formulation was 24 h. After one month of storage at 40 °C and 75 percent RH, the F2 formulation showed no noticeable change in physical as well as pharmaceutical performance characteristics.

Conclusion: Floating tablets of curcumin and berberine was successfully developed and passed on various pharmaceutical parameters.

Keywords: Curcumin, Berberine hydrochloride, HPMC K-100M, HPMC K-15M, Floating, Sodium bicarbonate, In Vitro Buoyancy

INTRODUCTION

Curcumin has been termed as a golden drug molecule as it finds its therapeutic application for various disease indications and serves as i.e., antioxidant, anti-inflammatory, anti-infective, anti-Alzheimer, anti-tumor, anti-diabetic, and anti-rheumatic agent [1, 2]. It has also been shown to be a hypoglycemic, hepatoprotective, nephroprotective, cardio-protective, and neuroprotective moiety [3]. It has also been reported to prevent myocardial infarction and suppresses thrombosis. It is the most popular polyphenol, very commonly consumed daily with food (in India, SAARC countries), which contributes to better compliance.

Berberine is a naturally occurring compound obtained from the bark, stem and roots of a number of clinically valuable medicinal plants, including Hydrastis Canadensis (goldenseal), Berberis Aristata (true turmeric), and Berberis vulgaris (barberry). Berberis Aquifolium (Oregon grape), It also possess activity against diabetes, hypertension, arrhythmia and serve also as anti-tumor, anti-fungal, anti-oxidative, anti-inflammatory, cerebro-protective agent [4, 5].

Curcumin and berberine both natural compounds are quite stable in acidic pH but have limited solubility requiring extra bit of time in stomach for complete dissolution and absorption leading to maximum bioavailability. Gastroretentive dosage forms (GRDFS) are a drug delivery formulation that is designed to remain in the gastric region for a long period and significantly prolong the gastric retention time (GRT) of drugs. A floating dosage unit is valuable drug delivery systems for drugs that act locally in the distal part of the stomach or proximal part of the intestine. It is also a good option for candidates, which are poorly soluble or unstable in intestinal fluids [6, 7]. So, we aimed at developing a floating drug delivery system for delivering curcumin and berberine simultaneously and also development of analytical UV spectroscopic method for simultaneous determination of both drugs.

MATERIALS AND METHODS

Drugs and reagents

The gift sample of Curcumin and Berberine hydrochloride was received from Alexi Pharmica, Baddl, Solan, and Himachal Pradesh, India. Analytical grade solvents were obtained from Rankem (Mumbai, India).

Equipments

These instruments double beam (Electronic India 2375, HP, India) UV visible spectrophotometer, Shimadzu ELB 300 electrical balance and (PCI analytics Pvt. Ltd) ultrasonic bath and dissolution tester (model EDT-08 Lx) which contain eight station was used for the purpose of simultaneous estimation.

Simultaneous estimation using UV method

From stock- I solutions of both drugs of curcumin and berberine HCl were prepared in solution. Further dilution of the stock solutions was concentration range at 2-12μg/ml of both drugs. The wavelength of maximum absorbance and absorbivity of both drugs to determined by the double beam UV spectrophotometer. The absorbance maxima of curcumin am 349 nm and berberine HCl are 420 nm. The absorbivity values of curcumin are (ax) 0.030 at 420 nm and (ax) 0.027 at 349 nm. And the absorptivity values of berberine HCl are (ay) 0.039 at 420 nm and (ay) 0.039 at 349 nm. And the absorptivity values of berberine HCl are (ay) 0.039 at 420 nm and (ay) 0.039 at 420 nm. The absorptivity values of both drugs replaced in following equation:

$$C = \frac{A_{2ay} - A_{ay}}{A_{xy} - A_{yxy}}$$
The average value was calculated hardness of the tablets. Ten tablets were accurately weighted and the average weight was determined. The equivalent weight of powder was withdrawn and was transferred to the 100 ml volumetric flask which contain 50 mg curcumin and 50 mg berberine hydrochloride. The powder dissolved the solvent and the further dilution of the solutions was prepared working standard concentration 5µg/ml of curcumin and 5 µg/ml of berberine hydrochloride [8, 9].

Analytical method validation

Validation is widely described as (ICH) establishing documented proof that a chosen operation can systematically produce a desired outcome or product that meets its predetermined requirements and quality characteristics. The objective of method validation is to confirm that the above said method will give reproducible and reliable results that could be utilized and are adequate for the required purpose. The process was validated using a variety of parameters, including linearity and range, specificity, precision, accuracy, and ruggedness, as well as LOQ and LOD.

Preparation of floating tablet by direct compression method (F1-F3)

Direct compression was used to render the floating tablets. Curcumin, berberine hydrochloride, and HPMC K15M were all weighed separately and passed through sieve No. 10 to obtain uniform size particles for efficient and homogeneous mixing. The powders were homogeneously mixed for half an hour. As a lubricant and anti-adhesive, talc and magnesium stearate were also combined in a fixed ratio. The homogeneous blend prepared was finally compresses using tablet punching machine (Table 1).

Table 1: Formulation table for floating tablets by wet granulation method

| S. No. | Ingredients       | F1 Quantity (mg) | F2 Quantity (mg) | F3 Quantity (mg) |
|--------|-------------------|------------------|------------------|------------------|
| 1      | Curcumin          | 50               | 50               | 50               |
| 2      | Berberine HCl     | 50               | 50               | 50               |
| 3      | HPMC K15M         | 40               | 60               | 80               |
| 4      | Sodium bicarbonate| 20               | 20               | 20               |
| 5      | Gum               | 15               | 15               | 15               |
| 6      | Citric acid       | 15               | 15               | 15               |
| 7      | Ethyl cellulose   | 10               | 10               | 10               |
| 8      | Aerosil           | 2.5              | 2.5              | 2.5              |
| 9      | Magnesium stearate| 2.5              | 2.5              | 2.5              |

Evaluation of floating tablets

Tablet thickness, stiffness, friability test, drug quality, and content uniformity were among the pharmaceutical parameters evaluated according to official compendia [10, 11].

Weight variation

A digital weighing balance was used to measure 20 tablets from formulation F1, F2 and F3 respectively, and the average weight was determined individually of the three different batches. The average weight was compared with the individual weight of all tablets of that particular batch [12].

Hardness

The Monsanto hardness tester was utilized determine the hardness of tablets. Ten tablets were taken and hardness was determined. The average value was calculated each of the batches [13].

Friability test

The percent friability was calculated using an Electrolab friabilator (USP). Ten tablets were accurately weighted before being placed in an Electrolab friabilator and rotated at 25 rpm for four minutes (100 revolutions) [12].

Drug content

The substance was dissolved in methanol and filtered through a 0.45 membrane after ten tablets were weighed individually. Using a double beam spectrophotometer UV 2375 electronics India, the absorbance was measured at 420 nm and 349 nm after sufficient dilution [12].

Content uniformity

Ten tablets were chosen at random and individually weighed and powdered. 50 mg of tablet powder was taken and was dissolved in 100 ml methanol. The solution was prepared followed by sonication for 15 min. The un-dissolved matter was filtered out. The absorbance of the diluted solutions was calculated at 420 nm and 349 nm respectively [13].

\[ Cy = \frac{A1ax2 - A2ax1}{ax2ay1 - axlay2} \]

Here, A1 and A2 are absorbance of combination tablet formulation of two drugs at 420 nm and 349 nm of both drugs separately. At first ten tablets were accurately weighted and the average weight was determined. The equivalent weight of powder was withdrawn and was transferred to the 100 ml volumetric flask which contain 50 mg curcumin and 50 mg berberine hydrochloride. The powder dissolved the solvent and the further dilution of the solutions was prepared working standard concentration 5µg/ml of curcumin and 5 µg/ml of berberine hydrochloride [8, 9].

Floating lag time (FLT)

Floating lag time was measured as the time it took for the tablet to rise to the surface and float. The tablet was kept in a 200 ml 0.1 N HCL solution (pH 1.2) at 37°C contained in a 250 ml glass beaker [14].

Total floating time

The cumulative floating time was measured as the amount of time the dosage formulation stayed continuously on the medium’s surface. The tablet was kept in a 200 ml 0.1 N HCL solution (pH 1.2) at 37°C contained in a 250 ml glass beaker. The total floating time was observed [15].

Swelling index

The ability of the polymer to swell and related floating time mainly depends on the contents of the stomach and the osmolarity of the medium. These ultimately have an effect on the release, delaying the action and extending the residence time. The individual tablets were weighed and were put in a beaker containing 200 ml of 0.1 N HCL. The tablet from the beaker was removed and was weighed every hour and the process was continued till constant weight was observed for subsequent three readings. The percent weight gain was calculated utilizing the formula [16].

\[ S . I . = \frac{(Wt - W0) \times 100}{W0} \]

W0 = is the initial weight of tablet, Wt = is the weight of the tablet at time t.

In vitro dissolution studies

0-Electro-lab dissolution apparatus was utilized with 900 ml 0.1 N HCL (pH1.2) solution at body temperature using USP paddle apparatus at 50 rpm for carrying out in vitro drug release studies of formulations. An aliquot of 5 ml is extracted from the solution and a fresh aliquot of 5 ml was added to it. The samples were taken at a fixed interval of time for up to 8 h. The sample was filtered, and 3 ml was taken from the filtrate. The absorbance of the solution was determined by using UV spectrophotometer at 420 nm and 349 nm and further the amount of drug release was calculated [17].
Release kinetics
The kinetics of drug release was studied using a variety of models. The obtained data were fitted into zero-order, first order, Higuchi model, and Korsemeyer Peppas release models to evaluate and characterize the release mechanism of drug and drug release kinetics of the dosage type [18].

RESULTS AND DISCUSSION
Simultaneous estimation using UV method
From stock I solutions of both drugs of curcumin and berberine, HCl was prepared in solution. Further dilution of the stock solutions was a concentration range at 2-12 µg/ml of both drugs. The wavelength of maximum absorbance and absorptivity of both drugs to be determined by the double beam UV spectrophotometer. The absorbance maxima of curcumin are 420 nm and berberine HCl are 349 nm (table 2).

Post compression parameters
The detailed results of weight variation, thickness, hardness, friability is mentioned in table 3. It was found the values were within the specified acceptable limit.

Swelling index
Water intake ratio or swelling index of formulations F1-F3 is given in table 3. The results clearly indicate that all three formulations have good swelling capability and the swelling index is linearly related to the concentration of the polymer used [19].

Table 2: Observation data of simultaneous method of both drugs

|          | Pure drug (µg/ml) | Absorbance | Absorptivity | Theoretical concentration (µg/ml) | Experimental concentration (µg/ml) |
|----------|------------------|------------|--------------|------------------------------------|-----------------------------------|
|          | 349 nm           | 421 nm     | Ax1          | Ax2                                |                                   |
| Curcumin | 2                | 0.007      | 0.006        | 0.0035                             | 0.003                             | 5 µg/ml                           | 4.55 µg/ml                       |
|          | 4                | 0.009      | 0.011        | 0.0022                             | 0.0027                            |                                   |
|          | 6                | 0.019      | 0.016        | 0.0031                             | 0.00266                           |                                   |
|          | 8                | 0.027      | 0.021        | 0.0033                             | 0.00262                           |                                   |
|          | 10               | 0.029      | 0.026        | 0.0029                             | 0.0026                           |                                   |
| Berberine hydrochloride | 2 | 0.041 | 0.007 | 0.0205 | 0.0035 | 5 µg/ml | 2.04 µg/ml |
|          | 4                | 0.079      | 0.011        | 0.019                              | 0.00275                           |                                   |
|          | 6                | 0.117      | 0.021        | 0.0195                             | 0.0035                            |                                   |
|          | 8                | 0.189      | 0.038        | 0.0236                             | 0.0047                            |                                   |
|          | 10               | 0.243      | 0.052        | 0.0243                             | 0.0052                            |                                   |

Table 3: Pharmaceutical parameters of formulations F1-F3

| Formulation | Weight variation (mg) | Tablet thickness (mm) | Hardness (kg/cm²) | Friability (%) |
|-------------|-----------------------|-----------------------|-------------------|---------------|
| F1          | 249±5                 | 4.04±0.5              | 4.5 kg/cm²        | 0.24%         |
| F2          | 251±5                 | 4.11±0.5              | 3.5 kg/cm²        | 0.28%         |
| F3          | 248±5                 | 4.00±0.5              | 5.0 kg/cm²        | 0.25%         |

(mean±SD, n= 3)

Floating lag time and total floating time

All the formulations have floating time within 30 sec to 12 min range. F1 formulation shows a minimum floating time 60 sec. floating lag time is depending on the amount of gas generating agents. Sometimes the amount of polymer also effects the floating lag time as the amount of polymers increased the floating lag time also increased but it was also found that the total floating time (TFT) also increased. The detailed data of floating lag time and (TFT) is mentioned in table 4. Total floating time depends on the amount of hydrophilic polymer in the formulation. The higher the amount it will remains float longer period of time. F2 batch float up to 10 hr while formulation F3 floated for more than 12 h which was desired for the sustained release dosage form [18].

Table 4: Pharmaceutical parameters of formulations F1-F3

| Formulation | Drug content (%) | Content uniformity (%) | Swelling index (%) | Floating lag time (sec) | Total floating time (h) |
|-------------|------------------|------------------------|--------------------|------------------------|------------------------|
| F1          | 94.20 and 93.18% | 97.05 and 92.70%       | 30.6±2.3           | 60±3                   | 8                      |
| F2          | 96.90 and 92.24% | 97.98 and 92.12%       | 36±1.56            | 240±4                  | 10                     |
| F3          | 95.78 and 91.29% | 96.80 and 92.35%       | 48.5±3.2           | 480±2                  | 12                     |

(mean±SD, n= 3)

Table 5: In vitro drug release data

| Time (min) | Percent release of berberine (f1) | Percent release of curcumin (f1) | Percent release of berberine (f2) | Percent release of curcumin (f2) | Percent release of berberine (f3) | Percent release of curcumin (f3) |
|------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|
| 0          | 0                                | 0                                | 0                                | 0                                | 0                                | 0                                |
| 15         | 14.88                            | 17.65                            | 12.07                            | 14.61                            | 17.21                            | 17.04                            |
| 30         | 39.71                            | 24.01                            | 30.73                            | 15.30                            | 33.54                            | 24.26                            |
| 60         | 51.69                            | 34.13                            | 39.65                            | 24.65                            | 46.04                            | 32.82                            |
| 120        | 61.42                            | 44.32                            | 49.88                            | 34.88                            | 55.33                            | 43.29                            |
| 180        | 64.31                            | 64.17                            | 56.09                            | 46.13                            | 63.03                            | 53.72                            |
| 240        | 80.99                            | 75.43                            | 65.54                            | 55.74                            | 68.63                            | 64.01                            |
| 300        | 87.48                            | 85.80                            | 75.35                            | 67.36                            | 78.64                            | 75.27                            |
| 360        | 90.90                            | 96.28                            | 80.65                            | 76.58                            | 86.04                            | 85.38                            |
In vitro drug release study

The optimized dissolution condition was applied for in vitro dissolution of Curcumin and Berberine Hydrochloride tablets. It was found that the prepared floating tablets were capable of releasing the drug in a sustained way for 8 h and the rate of release of drug was inversely proportional to the polymer utilized thus sustaining effect is directly related to polymer concentration. It was found that the drug delivery system was able to release both the drugs simultaneously and at a slower pace (table 5) [19, 20].

In vitro buoyancy studies

The results confirmed that the floating tablets formulated were able to provide the required buoyancy ability. F1 formulation containing minimum concentration was found to have floating lag time less than 2 min. The formulations started floating after a lag time and after that were buoyant for the study hours taken as detailed in table.

Table 6: Kinetics of curcumin release

| Formulation | Zero order | First order | Higuchi matrix | Korsmeyer peppas | Best fit model |
|-------------|------------|-------------|----------------|------------------|---------------|
|             | R²         | R²          | R²             | R²               |               |
| F1          | 0.964      | 0.915       | 0.989          | 0.976            | Higuchi plot  |
| F2          | 0.977      | 0.982       | 0.980          | 0.989            | Korsmeyer peppas |
| F3          | 0.954      | 0.968       | 0.992          | 0.982            | Higuchi plot  |

Table 7: Kinetics of berberine HCl release

| Formulation | Zero order | First order | Higuchi matrix | Korsmeyer peppas | Best fit model |
|-------------|------------|-------------|----------------|------------------|---------------|
|             | R²         | R²          | R²             | R²               |               |
| F1          | 0.837      | 0.970       | 0.958          | 0.948            | First order   |
| F2          | 0.888      | 0.975       | 0.981          | 0.958            | Higuchi plot  |
| F3          | 0.862      | 0.967       | 0.977          | 0.950            | Higuchi plot  |

Table 8: Results of stability study

| Formulation | Drug content (%) | Swelling index (%) | Floating lag time (sec) | Total floating time (h) | Content uniformity (%) |
|-------------|------------------|--------------------|-------------------------|-------------------------|------------------------|
| F1          | 92.19±3.08 and 91.87±3.96 | 32.7               | 90±4                    | 9                       | 94.04 and 91.70%       |
| F2          | 95.09±4.52 and 93.45±2.85 | 26.3               | 300±5                  | 10                      | 97.13 and 92.50%       |
| F3          | 94.1±3.35 and 96.88±4.89 | 31.3               | 450±2                  | 8                       | 96.70 and 93.20%       |

CONCLUSION

The results clearly revealed that the HPMC polymer-based tablets were able to achieve the floating time of more than 8 h and have the potential to enhance the bioavailability of drugs that are specifically absorbed from the stomach region by prolonging the residence time with sustained release in the stomach. It was discovered that floating drug delivery tablets with polymers for sustained release and a gas-producing agent were able to prolong the residence time of curcumin and berberine in the upper part of GIT where the drug is stable and better absorbed achieving the overall goal of better therapeutic efficacy of the product.

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AUTHORS CONTRIBUTIONS

All authors have contributed equally.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interest.

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