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# FORMULATION DEVELOPMENT AND IN VITRO EVALUATION STUDIES ON ORAL DISINTEGRATING TABLETS OF BROMHEXINE HYDROCHLORIDE BY USING NATURAL SUPER DISINTEGRANTS

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## ABSTRACT

The present study is an attempt to select best possible combination of diluents and disintegrants to formulate dispersible tablet of BromhexineHcl which disintegrates within few minutes there by reducing the time of onset of action.Mannitol is selected as diluents, natural gums such as guar gum, Karaya gum were selected as super disintegrants. Microcrystalline cellulose was used in all formulations. Aspartame as a sweetening agent, Magnesium stearate as a Lubricant.Guar gum is used as the super disintegrant in the formulation F1 – F3 at the concentrations of the 6, 10, 18 % respectively.Karaya gum is used as the super disintegrant in the formulation F4 – F6 at the concentrations of 6, 10, 18 % respectively.Direct Compression method was used to formulate the tablets.All the formulations were showed the acceptable values were found to be within the IP limits for precoprssed parameters .The percentage Drug content of all tablets was found to be between 98.3% - 102.2% of BromhexineHcl , which is within the limit.As the concentrations of the guar gum increases in the formulations F1 – F3 the disintegration time found to be decreased and the disintegration time for these formulations were 1.20, 1.09, 1.04 seconds respectively and the percentage drug release was also found to be increased for these formulations as 90.71, 94.97, and 98.21 % respectively. From the data obtained, it is observed from the formulation containing Guar gum - 18mg, Micro crystalline cellulose - 50mg in **Formulation F3**, shows Disintegration time in 1.04 mins and the Percentage drug release is of 98.21 % at the end of 30 min which satisfied all the tablet evaluation parameters for dispersible tablet. Hence looking at all the satisfactory parameters F3 batch is selected as the optimized batch.

**KEYWORDS:** oro dispersable tablets, super disintegrants, natural polymers, Dinsintergration time.

## INTRODUCTION

The oral route of drug administration is the important method of administering drug for systemic effects. Except in certain cases the parentral route is not routinely used for self administration e.g. insulin. The topical route of administration has only recently been developed to deliver drugs to the body for systemic effect. The parentral route of administration is important in treating medical emergencies in which the subject is coma or unable to swallow. Nevertheless at least 90% of all drugs used to provide systemic effect are administered by oral route. When a new drug is developed pharmaceutical company ask is whether or not the drug can be effectively administered for its intended effect by oral route of drug that are administered orally, solid oral dosage forms indicates the preferred class of product. Tablet and capsules indicates unit dosage forms in which usual dose of drug has been accurately placed.[1]

Tablet is defined as solid pharmaceutical dosage form containing drug substance with or with out suitable excipients and prepared by either compression or molding method. They have been widely used since the later part of the 19th century, and their popularity continues. The term compressed tablet is believed to have been used by wyeth and brother of Philadelphia. During this same period, molded tablet were introduced to use as hypodermic tablets for the preparation of solution for injection. Tablet remains popular as a dosage form because of the advantages both to the manufacturer (e.g. simplicity and economy of preparation, stability, and convenience in packing, shipping and dispensing) and patient (e.g. accuracy of dosage, compactness, portability, blandness of taste, and ease of administration). Although the basic medicinal approach for their manufacture has remained the same, tablet technology has gained great improvement. Effect are being made continually to understand more clearly the physical characteristics of powder compaction and the factor affecting the bioavailability of the drug from the dosage form after oral administration.[1,2]

Bromhexine is a substituted aniline that is 2,4-

dibromoaniline which is substituted at position 6 by a [cyclohexyl(methyl)amino]methyl group. It is used (as the monohydrochloride salt) as a mucolytic for the treatment of respiratory disorders associated with productive cough (i.e. a cough characterised by the production of sputum). It has a role as a mucolytic. It is a substituted aniline, a tertiary amino compound and an organobromine compound. It is a conjugate base of a bromhexine(1+).[6]

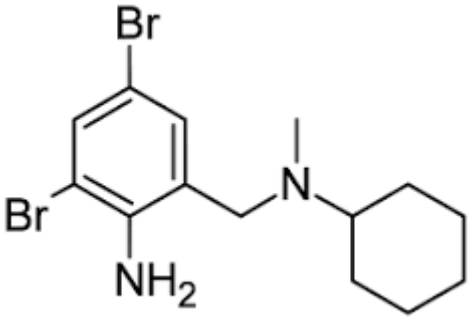


**Figure1: Chemical structure of Bromhexine.**

**Experimental work[5-10]**

Bromhexine HCl gift sample collected Avara chemicals Hyderabad from the, Guar gum, Karaya gum, Microcrystalline cellulose, Aspertame, Magnesium stearate, Mannitol SD fine chemicals Mumbai.

**METHODOLOGY**

**Pre-formulation studies**

**Organoleptic Properties**

The colour, odour and taste of the drug were recorded using descriptive terminology.

**Melting Point**

Capillary tube is used to determine the Melting point.

**Solubility Study**

It is important to know about solubility characteristic of a drug in aqueous system. Since they must possess some limited aqueous solubility to elicit a therapeutic response.The solubility of drug was recorded by using various descriptive terminology specified in Indian Pharmacopoeia, 2007.

**UV Spectrophotometric Study**

The absorption maximum of the test solution was observed between 200-400 nm region by using UV-Visible Spectrophotometer.

**Compatibility study**

A successful formulation of a stable and effective solid dosage form depends on careful selection of the excipients that are added to facilitate administration, promote the consistent release and bioavailability of the drug and protect it from degradation. If the excipients are new and have not been used in formulations containing the active substance, the compatibility studies are of paramount importance.

**FT-IR**

Compatibility of the Drug with the excipients was determined by subjecting the physical mixture of the drug and the polymers of the main formulation to infrared absorption spectral analysis. Any changes in chemical composition of the drug after combining it with the polymers were investigated with I.R. spectral analysis.

**Standard Calibration Curve of Bromhexine HCl**

Bromhexine Hcl was quantitatively analyzed by various techniques. In the present study, Bromhexine Hcl was estimated by UV spectrophotometry method.

**Determination of $\lambda_{max}$ for Bromhexine Hcl**

Two different stock solutions of drug sample were prepared by dissolving 100 mg of drug in 100.0 ml of Phosphate buffer were further diluted and analyzed spectrophotometrically to determine $\lambda_{max}$.

**Observation:**The $\lambda_{max}$ was found to be 246 nm.

**Preparation of standard calibration curve of Bromhexine Hcl In 0.1 N HCl**

Preparation of Phosphate buffer of 6.8 pH which is prepared by preparing stock solutions of 27.218 g of Potassium di hydrogen Phosphate in 1000ml and 0.2M NaOH i.e 8 gms of NaOH in 1000ml and adding 250ml of potassium di hydrogen Phosphate and 112 ml of sodium hydroxide stock solution and make up to 1000ml.

Preparation of dilutions for standard curve: Stock solution was prepared by dissolving 100.0 mg of BromhexineHcl in 100.0 ml of Phosphate buffer solutions, which was further diluted to give the solutions of concentration 2, 4, 6, 8 and 10 μg/ml respectively. Absorbance of these solutions were measured on UV spectrophotometer at 246 nm and plotted against the concentration to give the standard curve.

**Evaluation of Mixed Blend[38]**

**Bulk Density**

An accurately weighed powdered blend from each formula is introduced in to a measuring cylinder was shaken to remove any agglomerates. The volume occupied by the powder was measured which results in determining bulk volume bulk volume. It is determined using the following formula.

$$\text{Loose bulk density} = \frac{\text{Total weight of powder}}{\text{Total volume of powder}}$$

**Tapped bulk density (TBD)**

An accurately weighed powdered blend from each formula is introduced in to a measuring cylinder was shaken to remove any agglomerates.The measuring cylinder was tapped until no change in volume was noted which give the tapped volume. It is determined by using the following formula.

$$\text{Tapped bulk density} = \frac{\text{Total weight of powder}}{\text{Total volume of tapped powder}}$$

**Hausner's Ratio:**
It determined by using following formula
Hausner's Ratio = Tapped bulk density / Loose bulk density

A hausner ratio less than 1.25 shows good flow while greater than 1.5 shows poor flow.

**Carr's compressibility index**
It is a simple index that can be determined on little quantities of powder. The compressibility index of the formulation were determined by using following Carr's compressibility index equation.

**Method of manufacturing dispersible tablets**
**Formulation of dispersible tablets of Bromhexine HCl by using natural gums Karaya gum and Guar gums as super disintegrants.**
**Method:** Direct Compression Method Preparation of Bromhexine hcl (F1- F6) by using direct compression method: Composition of Bromhexine Hcl (F1 – F6).

**Table No: 1 Composition of Oral disintegrating tablets of Bromhexine HCl.**

| S.No | Ingredients (mg) | F1 | F2 | F3 | F4 | F5 | F6 |
|---|---|---|---|---|---|---|---|
| 1 | Bromhexine HCl | 100 | 100 | 100 | 100 | 100 | 100 |
| 2 | Guar gum | 6 | 10 | 18 | - | - | - |
| 3 | Karaya gum | - | - | - | 6 | 10 | 18 |
| 4 | Microcrystalline cellulose | 50 | 50 | 50 | 50 | 50 | 50 |
| 5 | Mannitol | 30 | 26 | 18 | 30 | 26 | 18 |
| 6 | Aspartame | 10 | 10 | 10 | 10 | 10 | 10 |
| 7 | Magnesium stearate | 4 | 4 | 4 | 4 | 4 | 4 |
| | TOTAL (mg) | 200 | 200 | 200 | 200 | 200 | 200 |

**Procedure**
Ingredients such as BromhexineHcl was sifted through 24 mesh, Microcrystalline cellulose was sifted through 40 mesh & ingredients such as Guar gum, Karaya gum, mannitol and aspartame, magnesium stearate, talc were passed through 60 mesh. The above ingredients were mixed in double cone blender for 25 mins and lubricants were added to the above ingredients. The lubricated blend was compressed by using oval shaped 9.5 punches.

**Evaluation of Bromhexine Hcl dispersible tablets[7,13]**
**Physico-Chemical Properties of Tablets**
**Hardness**
The hardness of tablets was determined by using Monsanto Hardness tester and it is expressed in $Kg/cm^2$. The whole experiment was performed in triplicate.

**Friability**
The friability of the tablet was determined by using Roche friabilator.It is expressed in percentage.Twenty tablets are initially weighed W1 and transferred into the friabilator. The friabilator was operated at 25 rpm for 4 minutes.The tablets were weighed again (W2). The percentage of friability was calculated by using following formula.
% Friability = Initial weight - Final weight x 100 / Initial weight

**Weight Variation**
20 tablets were selected randomly and weighed accurately. The weight divided by 20 provides an average weight of tablets. Not more than two of the individual weight deviates from the average weight by 10 % and none should deviate by more than double that percentage. Standard deviation and average weight were calculated.

**Uniformity of Content**
The drug content in each formulation was determined by mixing 10 tablets and powder equivalent to 10 mg was added in 100ml of pH 6.8 phosphate buffer followed by stirring for 10 minutes. The solution was filtered through a 0.45µ filter paper, diluted suitably and the absorbance of resultant solution was measured by using UV- Visible spectrophotometer at 246nm.

**Disintegration Test**
The test was carried out as per USP- 2008.

One tablet was placed in six tubes of the basket. Phosphate buffer of pH 6.8 is used as the disintegration medium.The temperature of the liquid was maintained at $37^0$ c ± $2^0$ c. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets, not less than 16 of total of 18 tablets should disintegrate completely.

**Wetting time**
A piece of filter paper folded twice and placed in a small petri dish containing 5ml of distilled water. The tablet was placed on the paper, and the time for complete wetting of the tablet was measured in seconds. The wetted tablet was then weighed. Wetting time, S, was determined by using following formula.
S = 10× Wb-Wa/Wb Where, Wa – weight of the tablet before water absorption.
Wb – weight of the tablet after water absorption.

**In- Vitro Drug Release Study[39]**
There are no standard methods yet developed for determining the in vitro drug release for dispersible tablets. The release rate of dispersible tablets of BromhexineHcl was carried out using rotating paddle apparatus (USP Type II). The dissolution medium

consisted of 900 ml of phosphate buffer (pH 6.8). The release study was performed at 37 $^0$C ± 0.5 $^0$C with a rotation speed of 50 rpm. The 5ml of sample was withdrawn at time interval of 5, 10, 15,20minutes up to 30 min and replaced with 5 ml of dissolution medium the amount of BromhexineHcl released was determined by UV Spectrophotometer at 246 nm.

**Table 2: Parameters were used for the dissolution study.**

| Apparatus | USP Dissolution apparatus (Type II) |
|---|---|
| Dissolution medium | Phosphate buffer (pH 6.8) |
| Temperature | 37±0.5 °C |
| Volume | 900 ml |
| Speed | 50 rpm |
| Sample withdrawn | 5 ml |
| Running Time | 30 min |

**DRUG iRELEASE iKINETICS**
Zero iorder ikinetics
First iorder ikinetics
Higuchi imodel
Korsmeyer iand iPeppa's imodel
Hixson iand iCrowell ierosion iequation

**RESULTS AND DISCUSSION**
**Identification of Drug**
Organoleptic properties:
Colour: White or slightly yellow.
Odour: Odourless.
Taste: Tasteless.
Nature: crystalline powder.

**Melting Point**
232.7$^o$c

**Solubility Study**
Sparingly soluble in water, Soluble in methyl alcohol, Practcally insoluble in methylene chloride

**standard calibration curve of Bromhexine Hcl**

Serial of dilutions are made from standard working solution with distilled water to get concentration from 20 to 100 microgram ⁄ ml and the absorbance was measured at 246nm.

**Table No: 3 Standard Calibration curve of Bromhexine Hydrochloride.**

| S.No | Concentration (mcg/ml) | Absorbance |
|---|---|---|
| 1 | 20 | 0.104 |
| 2 | 40 | 0.216 |
| 3 | 60 | 0.344 |
| 4 | 80 | 0.464 |
| 5 | 100 | 0.599 |

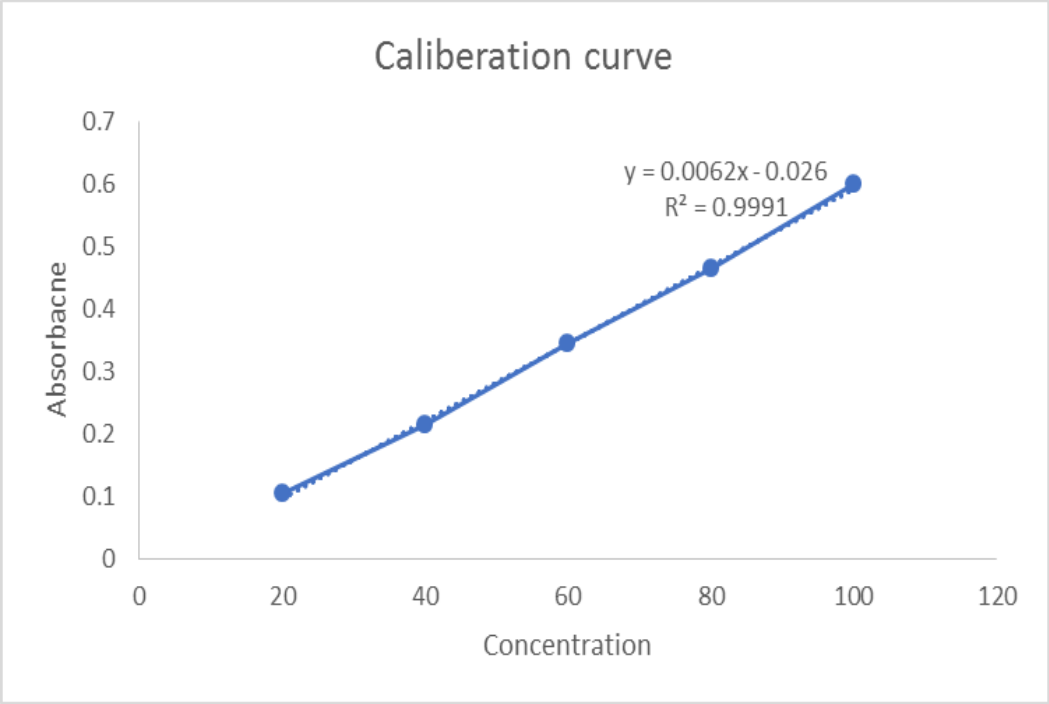


**Figure 2:caliberation curve of Bromhexine Hydrochloride.**

**Micromeritic properties to the Bromhexine oro dispersible tablets**

The results of the Micromeritic properties of the granules are presented in table No:4.

**Table No. 4: Micromeritic properties of BromhexineHCl Dispersible tablets.**

| Form. No | Angle of repose (θ°) | Bulk density (gm/cm3) | Tapped density (gm/cm3) | Compressibility Index (%) | Hausner Ratio |
|---|---|---|---|---|---|
| F1 | 22.33 | 0.425 | 0.464 | 8.60 | 1.094 |
| F2 | 22.29 | 0.416 | 0.459 | 9.36 | 1.103 |
| F3 | 24.15 | 0.425 | 0.465 | 8.60 | 1.094 |
| F4 | 23.48 | 0.421 | 0.459 | 8.27 | 1.090 |
| F5 | 25.26 | 0.431 | 0.470 | 9.57 | 1.105 |
| F6 | 22.78 | 0.425 | 0.481 | 10.60 | 1.118 |

The Bulk density of various powder mixed blends prepared with different superdisintegrants, was measured by graduated cylinder. The bulk density was found in the range **0.416– 0.431 kg/cm$^3$.**

The Tapped density of various powder mixed blends prepared with different superdisintegrants, was measured by graduated cylinder. The Tapped density was found in the range **0.459– 0.481 gm/cm$^3$.**

The Compressibility index of various powder mixed blends, prepared with different superdisintegrants, using bulk density and tapped density data, compressibility index was calculated. It was found in the range **8.27 – 10.60%.**

The Hausner's ratio of various powder mixed blends, prepared with different superdisintegrants, using bulk density and tapped density data, Hausner's ratio was calculated. It was found in the range **1.090 – 1.118.**

Angle of repose ranged from **22.29-25.26.** The flow properties of powder blend in all formulations exhibit good flow characteristics.

**Appearance of the tablet**

White colored, oval uncoated, molted tablet with plain surface on two side.

**Physical Evaluation of the Bromhexine HCl Oro dispersible tablets**

The result of the Physico-chemical properties of the prepared tablets was done as per the procedure and presented in the table no: 17.

**Table No -5: Physical Evaluation of the BromhexineHcl orodispersible tablets.**

| Form. No | Weight variation in mg | Hardness (Kg/cm2) | Friability (%) | Disintegration time (min) | Uniformity of content | Wetting time (sec) |
|---|---|---|---|---|---|---|
| F1 | 202±7.5 | 3.50 | 0.293 | 1.20 | Pass | 54.55 |
| F2 | 200±7.5 | 3.48 | 0.293 | 1.09 | Pass | 55.86 |
| F3 | 201±7.5 | 3.42 | 0.291 | 1.04 | Pass | 54.47 |
| F4 | 205±7.5 | 3.58 | 0.428 | 1.25 | Pass | 56.37 |
| F5 | 199±7.5 | 3.68 | 0.426 | 1.19 | Pass | 59.35 |
| F6 | 200±7.5 | 3.71. | 0.426 | 1.13 | Pass | 54.29 |

**Evaluation of BromhexineHcl tablets**

Tablets were prepared using direct compression technique. Since the material was free flowing, tablets were obtained of uniform weight due to uniform die fill tablets were obtained in the range with acceptable weight variations as per pharmacopoeia specifications, less than **5%.**

Tablets were evaluated by using Vernier calliper. The thickness of the tablets was found in the range **5.2 – 6.0 mm**. Uniformity thickness was obtained due to uniform die fill. Tablets were evaluated by using Pfizer Hardness tester. Hardness of the tablets was found in the range **3.36 – 3.71 Kg/cm$^2$.** Uniform hardness was obtained due to equal compression force.

Tablets were evaluated by using Roche Friabilator and friability of tablets was observed in the range **0.291 - 0.530.**

Tablets were evaluated for disintegration time in the IP disintegration apparatus. The disintegration time was found in the range **29 – 33 sec.**

The tablets are evaluated for the uniformity dispersion in which all the tablets were dispersed in few seconds in purified water and all the formulations were under the IP limits.

Tablets were evaluated for wetting time test. The wetting time was found in the range **54 – 59 sec.**

Tablets are evaluated for the content uniformity test all the formulations are under the IP specifications.

**Assay of prepared Bromhexinedispersible tablets:**

The results of the assay of BromhexineHcl were done as per procedure and presented in the table no: 18.

**Table No: 6 Assay of prepared Bromhexinedispersible tablets.**

| Formulation No | Assay of Bromhexine Hcl in % w/w |
|---|---|
| F1 | 98.3 |
| F2 | 98.6 |
| F3 | 99.0 |
| F4 | 101.7 |
| F5 | 101.5 |
| F6 | 102.2 |

Tablets were evaluated by using assay method. The drug was obtained in the acceptable limit. The drug content was found in the range **98.3 – 102.2%.**

**In–vitro drug release studies In–vitro drug release of Bromhexine HCl**

**Table No: 7: In Vitro Dissolution Profile of Bromhexine Hcl dispersible tablets in pH6.8 Buffer Solution.**

| Time in mins | F1 | F2 | F3 | F4 | F5 | F6 |
|---|---|---|---|---|---|---|
| 5 | 52.45 | 54.78 | 59.31 | 53.28 | 55.46 | 60.71 |
| 10 | 66.44 | 67.80 | 72.54 | 70.78 | 69.80 | 79.88 |
| 15 | 71.70 | 74.70 | 81.20 | 76.54 | 82.88 | 87.91 |
| 20 | 81.89 | 83.10 | 89.13 | 83.72 | 91.43 | 92.14 |
| 25 | 89.92 | 90.89 | 93.67 | 87.78 | 93.58 | 95.13 |
| 30 | 90.71 | 94.97 | 98.21 | 91.12 | 94.45 | 97.99 |

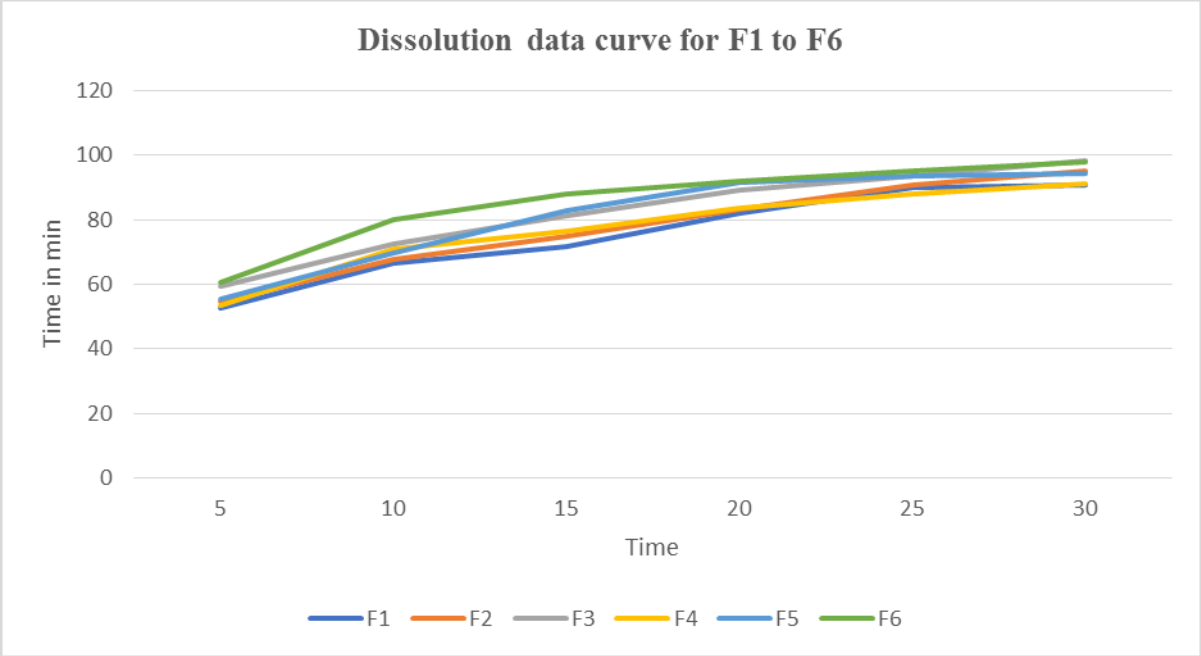


**Figure 3: In vitro Dissolution studies of Bromhexine Hcl disintegrating tablets formulations F1-F6.**

Invitro drug release studies were conducted for the formulation using USP dissolution apparatus type-II (paddle), at 50 rpm. The percentage drug release at the end of 30 min was found in the range **90 – 98 %.**

**Kinetics study**

**Table 8: Dissolution Kinetics of optimized batch F3.**

| TIME | SQRT | LOG TIME | % DRUG REL | LOG % D REL | % D REM | LOG % D REM |
|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 100 | 2 |
| 5 | 2.236068 | 0.69897 | 59.31 | 1.7731279 | 40.69 | 1.60948769 |
| 10 | 3.162278 | 1 | 72.54 | 1.8605776 | 27.46 | 1.438700533 |
| 15 | 3.872983 | 1.176091 | 81.2 | 1.909556 | 18.8 | 1.274157849 |
| 20 | 4.472136 | 1.30103 | 89.13 | 1.9500239 | 10.87 | 1.036229544 |
| 25 | 5 | 1.39794 | 93.67 | 1.9716005 | 6.33 | 0.80140371 |
| 30 | 5.477226 | 1.477121 | 98.21 | 1.9921557 | 1.79 | 0.252853031 |

## DISCUSSION

The release profile of the optimized formula F3 fitted best to Korsmeyer- Peppas model with $R^2$ value of 0.998. As the n value for the Korsmeyer-Peppas model was found to be less than 0.45, it follows Fickian transport.

## SUMMARY AND CONCLUSION

The study was carried to formulate and evaluate dispersible tablet dosage form containing Bromhexine Hcl as a mucolytic drug.

The present study is an attempt to select best possible combination of diluents and disintegrants to formulate dispersible tablet of BromhexineHcl which disintegrates within few minutes there by reducing the time of onset of action.

Mannitol is selected as diluents, natural gums such as guar gum, Karaya gum were selected as super disintegrants. Microcrystalline cellulose was used in all formulations. Aspartame as a sweetening agent, Magnesium stearate as a Lubricant.

Guar gum is used as the super disintegrant in the formulation F1 – F3 at the concentrations of the 6, 10, 18 % respectively.

Karaya gum is used as the super disintegrant in the formulation F4 – F6 at the concentrations of 6, 10, 18 % respectively.

Direct Compression method was used to formulate the tablets.

All the formulations were showed the acceptable flow properties and the precompression parameters like Bulk density, Tapped density and Hausner ratio.

The post compression parameters like Hardness, Friability, Disintegration time, Weight variation, wetting time, Dispersion time values were found to be within the IP limits.

The percentage Drug content of all tablets was found to be between 98.3% - 102.2% of BromhexineHcl , which is within the limit.

As the concentrations of the guar gum increases in the formulations F1 – F3 the disintegration time found to be decreased and the disintegration time for these formulations were 1.20, 1.09, 1.04 seconds respectively and the percentage drug release was also found to be increased for these formulations as 90.71, 94.97, and 98.21 % respectively. From the above results it was found that as the concentration of guar gum increased and microcrystalline cellulose decreases the disintegration and dissolution time was found to be improved, so considering the above results it was found that the F3 batch was found to be optimized batch and it pass all the preformulation parameters and evaluation results as per the IP limits

From the data obtained, it is observed from the formulation containing Guar gum - 18mg, Micro crystalline cellulose - 50mg in **Formulation F3**, shows Disintegration time in 1.04 mins and the Percentage drug release is of 98.21 % at the end of 30 min which satisfied all the tablet evaluation parameters for dispersible tablet. Hence looking at all the satisfactory parameters F3 batch is selected as the optimized batch.

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