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# FORMULATION & *IN VITRO* EVALUATION OF GASTRORETENTIVE FLOATING DRUG DELIVERY SYSTEM OF MEBHYDROLIN NAPADISYLATE

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## ABSTRACT

Gastro retentive drug delivery systems (GRDDS) are the systems which are retained in the stomach for a longer period of time and thereby, improve the bioavailability of drugs. The objective of this study was to formulate gastro retentive floating matrix tablet of Mebhydrolin Napadisylate using different ratios of HPMC K4M & HPMC K100LV. The sodium bi carbonate and citric acid was used in combination as gas generating agent. The tablets were prepared by wet granulation method and evaluated for the pre and post compression parameters such as angle of repose, tapped density, bulk density, Carr's Index, Hausner's ratio, hardness, friability, weight variation, thickness, swelling index, *In vitro* buoyancy studies and *In vitro* drug release studies. The tablets containing Mebhydrolin Napadisylate released 61.6 to 87.6% of drug at the end of 10 hrs by *In vitro* release study. Formulation F3 containing HPMC K4M and HPMC K100LV at a ratio of 1:1 found to be the best formulation in terms of drug release and *In vitro* buoyancy time. The drug release followed the Higuchi model controlled mechanism of tablet Mebhydrolin Napadisylate. FTIR spectrums obtained suggest that there was no significant chemical interaction between the polymers and drug.

**KEYWORDS**: GRDDS, Mebhydrolin Napadisylate, HPMC K4M, HPMC K100LV, Sodium bi carbonate

## INTRODUCTION

Oral drug delivery is the virtually desirable and best liked means of administering therapeutic agents for their therapeutic effects. The steep level of patient compromise in laying hold of oral dosage forms is due to the ease of administration, patient compromise, ability in formulation and handling of these forms.[1] However the oral route of administration that be suffers mutually unquestionable limitations one as short residence time of the dosage comprise in the gastrointestinal tract, unpredictable gastric emptying, degradation of the drug what is coming to one to intensively reactive nature of gastrointestinal contents and existence of an absorption window in the gastric and upper small intestine for several drugs.[2], [3] Several approaches are currently used to retain the dosage in the stomach. These boost bioadhesive system[8], swelling and expanding systems[11], [12], floating systems[5], [6] and other delayed gastric emptying devices.[14], [15] Floating dosage forms are dosage forms mutually a bulk density lower than that of the gastric content. These manage them to remain buoyant on the surface of the gastric content for a unassailable period of time without affecting the intrinsic rate of emptying. They are further referred to as hydro dynamically balanced system (HSB) as they are able to uphold their low density.

Gastro retentive floating tablets are designed based on gas generating principle. Design of floating tablets needs a strong matrix forming polymer, a gas generating agent and a floating enhancer one as beeswax. Several polymers one as at variance viscosity grades of HPMC, Carbopol 934P, Eudragits, calcium alginate, Chitosan, Xanthan gum, Ethyl cellulose etc., have been used in the design of floating tablets of distinct API. Sodium bi carbonate is preferred gas generating agent in the formulation of floating tablets.

Mebhydrolin, an ethylenediamine derivative, is 1st generation sedating Histamine H1 receptor antagonist with muscarinic and sedative properties. It has been given orally as the Napadisylate salt for the symptomatic relief of allergic diseases or symptoms a well known as Urticaria, Hay fever, pruritus of distinctive origins, allergic conjunctivitis, Dermatitis of nutritional origin, Vasomotor Rhinitis, Allergic Asthma. The usual dose of Mebhydrolin 50mg two to six tablets daily is required. Gastro retentive floating tablets of Mebhydrolin were designed in the present study to advance sustained release and to enhance its absorption and bioavailability.

## MATERIALS AND METHODS

### Materials

Mebhydrolin Napadisylate was obtained as a gift sample from Beximco Pharmaceutical Ltd., Bangladesh. Povidone K-30, Polyvinyl alcohol, Lactose, Sodium bi carbonate, Citric acid were purchased from Taj Scientific, Chittagong. Hydropropyl methylcellulose K4M (HPMC K4M) and HPMC K100LV were purchased from K.R. Scientific Traders, Dhaka. All other materials used were of Pharmacopoeial grade.

### Preparation of Gastro Retentive Floating Tablets of Mebhydrolin Napadisylate

The gastro retentive tablets were prepared by wet granulation method using different ratios of polymers (HPMC K4M and HPMC K100LV) as described in Table1. The polymers ratios were designed in order to evaluate the effect of HPMC K100LV on the activity of HPMC K4M. Povidone K30 and Polyvinylalcohol were used as granulating agent and binder respectively. Citric acid and sodium bi carbonate were used as gas generating agent. Lactose was used as diluents. Drug and all the Excipients except Mg-stearate and talc were blended geometrically in mortar and pestle and the granulating agent was added. Granules were obtained by passing the mass through sieve no.12 the resulting granules were dried at 60°C for 4 hours. Then the dried granules were passed through sieve no.30 and finally Mg-stearate and talc were added and mixed for lubrication purpose. The dried granules so obtained were compressed into tablets using single punch tablet compression machine. Seven formulations were prepared and coded as F1 to F7. All the formulations contain 100mg of Mebhydrolin Napadisylate.

**Table 1: Different ratios of the polymers**

| FC | HPMC K4M:HPMC K100LV |
|---|---|
| F1 | 1:0 |
| F2 | 0:1 |
| F3 | 1:1 |
| F4 | 1:0.75 |
| F5 | 1:0.50 |
| F6 | 1:0.25 |
| F7 | 1:2 |

**Table 2: Composition of Mebhydrolin Napadisylate gastro retentive floating tablet (F1-F7)**

| Batches/Ingredients | F1 | F2 | F3 | F4 | F5 | F6 | F7 |
|---|---|---|---|---|---|---|---|
| **Mebhydrolin Napadisylate** | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| **HPMC K4M** | 95 | -- | 47.5 | 54.29 | 63.33 | 76 | 31.67 |
| **HPMC K100LV** | -- | 95 | 47.5 | 40.71 | 31.67 | 19 | 63.33 |
| **Povidone K-30** | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| **Polyvinyl alcohol** | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| **Lactose** | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| **Na-bi-carbonate** | 12 | 12 | 12 | 12 | 12 | 12 | 12 |
| **Citric acid** | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| **Mg-stearate** | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| **Talc** | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| **Total** | 250 | 250 | 250 | 250 | 250 | 250 | 250 |

***Note:*** *All the quantities are expressed in terms of milligrams.*

**Pre Compression Parameters Evaluation of Mebhydrolin Napadisylate Floating Tablet**

Before going into compression different parameters of all the batches were evaluated. Angle of repose, bulk density, tapped density, Carr's index, Hausner's ratio were evaluated.

**Angle of Repose (Ɵ):** The frictional forces in a loose powder or granules can be measured by the angle of repose.

$\tan \theta = h / r$

$\theta = \tan^{-1} (h/r)$

Where, θ is the angle of repose, h is height of pile and r is radius of the base of pile

**Bulk density and Tapped density:** Both bulk density and tapped density were determined and calculated using following formula:

Bulk density= Bulk volume of the powder/Weight of the powder

Tapped density= Tapped volume of the powder/Weight of the powder

**Carr's index:** Percentage compressibility of powder mix was determined by Carr's compressibility index. Carr's index was calculated by the following formula.

Carr's index (%) = [(Tapped density-Bulk density) ×100]/Tapped density

**Hausner's' ratio:** Hausner's ratio was calculated by following formula

Hausner's ratio=Tapped density/Bulk density

**Post compression parameters evaluation of Mebhydrolin Napadisylate floating tablet**

**Weight variation test:** [20] Twenty tablets from each formulation were selected randomly and weighed individually, average weight was determined. Then the percent of weight variation is determined by following way-

% of Weight variation= [(Individual weight-average weight) ×100]/Average weight

**Hardness test**:[20] The resistance of tablets to shipping or breakage under the condition of storage, transportation and handling before usage depends on its hardness. The hardness of the tablet was determined by Monsanto hardness tester. The hardness was measured in terms of $kg/cm^2$.

**Friability**: The friability of the tablet was determined by Roche friabilator. Ten tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25rpm, the tablets were weighed and the percentage loss in tablet weight was determined.

***In vitro* Buoyancy study**[21] The in vitro buoyancy was determined by floating lag time. The tablets were placed in a 100ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface for floating was determined as Floating Lag Time (FLT) and the time period up to which the tablet remained buoyant was determined as Total Floating Time (TFT).

**Swelling Study**[22] The swelling behavior of a dosage unit was measured by studying its weight gain. The swelling index of tablets was determined by placing the tablets in the basket of dissolution apparatus and the dissolution medium was 900 ml 0.1N HCl (pH 1.2) at 37±0.5° at 50 rpm. After one, two, three, four and five, each dissolution basket containing tablet was withdrawn and blotted with tissue paper to remove the excess water and weighed on the analytical balance. The experiment was performed in triplicate for each time point. Swelling index was calculated by using the following formula-

Swelling index= [(Wet weight of tablet-Dry weight of tablet) ×100]/Dry weight of tablet

***In vitro* release studies**

In vitro release studies of all the floating formulation of Mebhydrolin Napadisylate were performed by using a USP Type II (Paddle) apparatus at a rotational speed of 50rpm. Exactly 900 ml of 0.1N HCl was used as the dissolution medium and the temperature was maintained at 37°C±0.5°C.

**Drug release kinetics**

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero order[30], first order[31] and Higuchi release model.[32]

The drug release data were fitted to models representing zero order (cumulative amount of drug release vs. time), first order (log percentage of drug remaining vs. time) and Higuchi's (cumulative percentage of drug released vs. square root of time) kinetic to know the release mechanisms.

**Compatibility study**

IR spectra were obtained for pure drug Mebhydrolin and drug with exipients. The sample pellet was mounted in IR compartment and scanned at wavelength 4000$cm^{-1}$-600$cm^{-1}$at an ambient temperature.

**RESULT AND DISCUSSION**

**Standard calibration curves of Mebhydrolin Napadisylate**

Six different concentration of standard Mebhydrolin Napadisylate namely 10, 20, 40, 60, 80 and 100 µg/ml were prepared by using 0.1N HCl. Then the absorbance of each solution is measured at 287nm by using Shimadzu UV visible spectrophotometer.[35] Data obtained from the standard curve preparation shows in table 2 and Figure 1 shows the standard calibration curve for the Mebhydrolin Napadisylate with regression value.

**Table 3: Standard calibration curve at 287 nm**

| Concentration(µg/ml) | Absorbance (Å) |
|---|---|
| 10 | 0.04 |
| 20 | 0.052 |
| 40 | 0.068 |
| 60 | 0.079 |
| 80 | 0.092 |
| 100 | 0.103 |

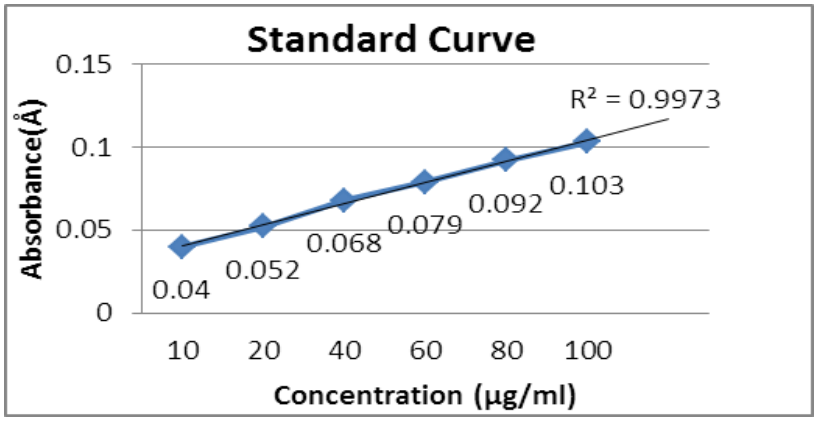


**Figure 1: Standard calibration curve at 287 nm**

**Pre compression Parameters**

Results of the pre-compression parameters performed for the Mebhydrolin Napadisylate granules formulations F1 to F7 are tabulated in Table 3.

**Angle of repose:** The values were found to be in the range of 25.033° to 28.8°. All the formulation showed angle of repose below 30° which is the indication of a good flow property of the granules.

**Carr's index:** Carr's index lies within the range of 10.04±0.276225 to 16.49667±0.427824. All the formulations show good compressibility.

**Hausner's ratio:** Hausner's ratio was found to be in the range of 1.128667±0.001528 to 1.359±0.321314.

**Bulk density and Tapped density:** The bulk density and tapped density for all formulations was found in the range of 0.283333±0.005774 to 0.53±0.01 g/cm$^3$ and 0.323333±0.015275 to 0.683333±0.005774 g/cm$^3$.

**Table 4: Pre compression parameters of designed batches (F1-F7)**

| FC | Bulk Density(g/cm$^3$) | Tapped Density(g/cm$^3$) | Carr's Index (%) | Hausner's Ratio | Angle of Repose(°) |
|---|---|---|---|---|---|
| **F1** | 0.28±0.006 | 0.34±0.015 | 15.79±0.377 | 1.18±0.003 | 28.8±0.721 |
| **F2** | 0.32±0.01 | 0.39±0.015 | 12.85±0.41 | 1.15±0.004 | 26.77±0.611 |
| **F3** | 0.35±0.006 | 0.41±0.015 | 14.51±0.413 | 1.36±0.321 | 27.77±0.945163 |
| **F4** | 0.38±0.01 | 0.45±0.015 | 12.97±0.603 | 1.13±0.002 | 25.03±0.503 |
| **F5** | 0.28±0.015 | 0.32±0.015 | 13.84±0.672 | 1.16±0.004 | 28.47±0.451 |
| **F6** | 0.53±0.01 | 0.68±0.006 | 16.50±0.428 | 1.29±0.004 | 26.53±0.451 |
| **F7** | 0.34±0.012 | 0.39±0.015 | 10.04±0.276 | 1.18±0.003 | 27.3±0.2 |

***Note:*** *All data represent as Mean ± SD.*

**Post compression parameters**

All of the Mebhydrolin Napadisylate formulations were tested for Physical parameters like Weight Variation, Hardness and Friability were tabulated in Table 4. The results of the physical tests of many of the formulation were within the limits and comply with the standards.

**Weight Variation:** All the tablets passed weight variation test as the weight variation was within the Pharmacopoeial limits of ±10% of the weight.

**Hardness test:** The hardness of all formulations was in the range of 4.6±0.3 to 6.6±0.3 kg/cm$^2$.

**Friability test:** The friability values of prepared tablets ranged from 0.34±0.015 to 0.77±0.02%. The friability was below 1% for all formulations, which is an indication of good mechanical resistance of the tablets.

**Table 5: Post compression parameters of designed batches (F1-F7)**

| FC | Average Weight (mg) | Hardness(kg/cm$^2$) | Friability (%) |
|---|---|---|---|
| **F1** | 256.33±1.155 | 5.33±0.152 | 0.56±0.03 |
| **F2** | 247.83±1.041 | 4.6±0.3 | 0.76±0.03 |
| **F3** | 249.5±0.866 | 5.65±0.229 | 0.35±0.036 |
| **F4** | 244.67±1.528 | 6.6±0.3 | 0.47±0.02 |
| **F5** | 256.17±1.258 | 4.72±0.236 | 0.77±0.02 |
| **F6** | 258.67±1.155 | 5.6±0.3 | 0.69±0.03 |
| **F7** | 243.17±2.255 | 6.3±0.1 | 0.34±0.015 |

***Note:*** *All data represent as Mean ± SD.*

***In vitro* Buoyancy Studies**

In vitro buoyancy of the tablets from each formulation (F1 to F7) was determined and the results are mentioned in Table 6. Where, the highest and lowest floating lag time (FLT) was observed with the formulation F5 and F1 respectively and the highest and lowest total floating time (TFT) was observed with the formulation F3 and F5 respectively. The amount of HPMC K100LV plays a vital rule in the buoyancy properties of the formulations. As the amount of HPMC K100LV in the polymers ratio increases it decreases the FLT and increases the TFT.

**Swelling Index**

The swelling index of the formulations was evaluated and the results are mentioned in Table 6. Where, the highest and lowest swelling was observed with the formulation F3 and F5 after 5 hours respectively. The swelling index increases by increasing the contact time with the 0.1N HCl buffer, as the polymer gradually absorbs buffer due to hydrophilic nature of the polymer, resultant swelling of the tablets is also observed.

**Table 6: Results obtained from swelling index and Buoyancy studies**

| FC | Swelling index | Buoyancy Lag Time(Sec.) | Total Floating Time (hrs.) |
|---|---|---|---|
| **F1** | 39.85 | 112 | 2.5 |
| **F2** | 79.06 | 98 | >24 |
| **F3** | 85.69 | 60 | >15 |
| **F4** | 83.43 | 78 | 12 |
| **F5** | 60.69 | 85 | 9 |
| **F6** | 59.81 | 91 | 8 |
| **F7** | 89.79 | 95 | >24 |

***In vitro* Release study**

In vitro release studies of all gastro retentive floating tablets formulations of Mebhydrolin Napadisylate were carried out in 0.1N HCl. The study was performed for 10 hours and cumulative drug release was calculated at every one hour time interval and the results were mentioned in Table 7. The highest release after 10 hours of release study was observed for formulation F3 which contain the polymer ratio (HPMC K4M: HPMC K100LV) of 1:1.

**Table 7: Results obtained from *In vitro* release study**

| FC/Time (hrs.) | F1 | F2 | F3 | F4 | F5 | F6 | F7 |
|---|---|---|---|---|---|---|---|
| 1 | 17.2 | 18.3 | 26.1 | 21.6 | 20.5 | 19.9 | 12.2 |
| 2 | 21.6 | 22.7 | 29.4 | 28.3 | 25.5 | 23.9 | 16.1 |
| 3 | 26.1 | 27.2 | 37.7 | 35.5 | 32.7 | 32.2 | 21.07 |
| 4 | 28.9 | 31.6 | 41.1 | 43.8 | 37.2 | 37.2 | 28.3 |
| 5 | 33.8 | 39.9 | 51.1 | 47.2 | 44.4 | 44.3 | 33.8 |
| 6 | 37.7 | 46.1 | 58.3 | 53.3 | 50.5 | 49.4 | 39.9 |
| 7 | 41.6 | 50.5 | 66.1 | 60.5 | 54.4 | 51.6 | 46.6 |
| 8 | 46.6 | 53.8 | 73.2 | 69.8 | 62.7 | 58.3 | 51.6 |
| 9 | 53.8 | 58.3 | 80.9 | 74.9 | 69.9 | 64.4 | 57.1 |
| 10 | 63.3 | 61.6 | 87.6 | 78.8 | 71.6 | 68.8 | 66.1 |

**Drug Release Kinetics**

The drug release data were fitted to models representing zero order (cumulative % drug release vs. time), first order (log % drug release vs. time) and Higuchi's (cumulative % drug

release vs. square root of time) to know the release kinetics. The results of all formulations were shown in Table 8. All the formulations followed the zero order release kinetics. The release kinetics zero, first and Higuchi's were shown in Figure 2, Figure 3, Figure4 respectively.

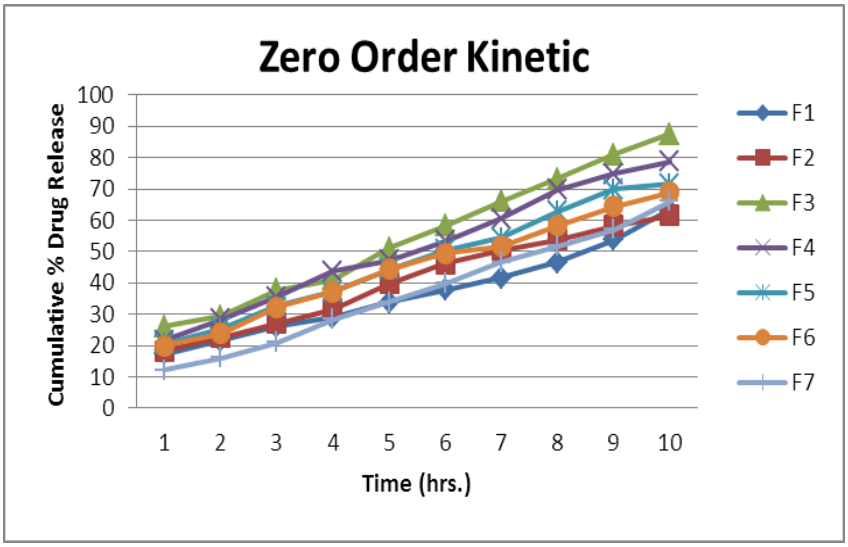


**Figure 2: Zero order release kinetic of all floating formulations (F1 to F7)**

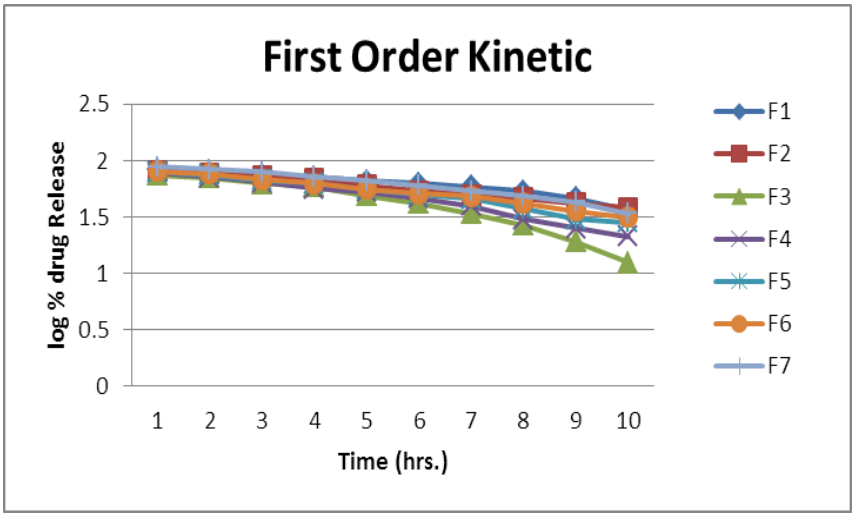


**Figure 3: First order release kinetic of all floating formulations (F1 to F7)**

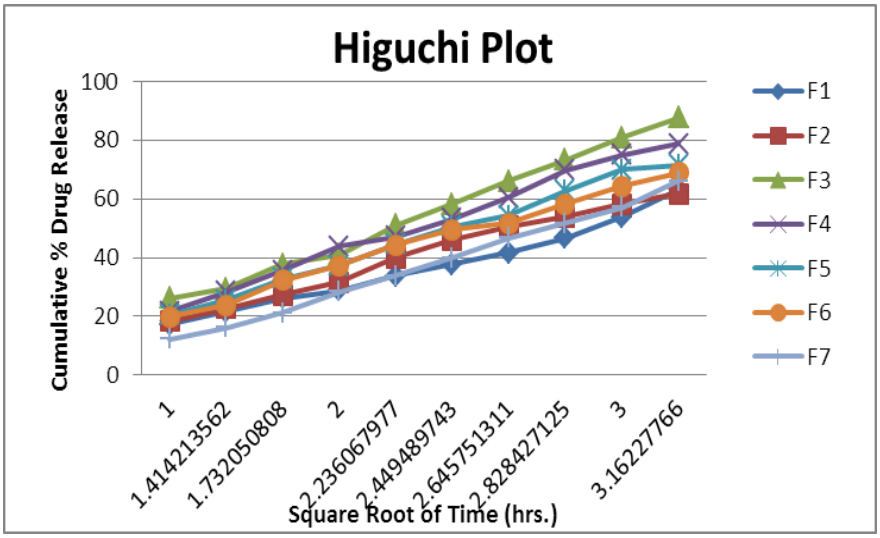


**Figure 4: Higuchi's release kinetic of all floating formulations (F1 to F7)**

**Table 8: Regression Values For different formulations**

| FC | Regression values | | |
|---|---|---|---|
| | Zero order | Higuchi's plot | First order |
| **F1** | 0.976 | 0.976 | 0.926 |
| **F2** | 0.989 | 0.989 | 0.992 |
| **F3** | 0.994 | 0.994 | 0.928 |
| **F4** | 0.995 | 0.995 | 0.969 |
| **F5** | 0.995 | 0.995 | 0.975 |
| **F6** | 0.993 | 0.993 | 0.985 |
| **F7** | 0.996 | 0.996 | 0.967 |

**Compatibility Study**

Potential chemical interaction between drug and exipients may change the therapeutic efficacy of the drug. IR spectroscopy for pure drug and drug-exipients were carried out for the optimized formulation. The spectrums obtained suggest that there was no chemical interaction between the drug and exipients (polymers). The spectrums of pure drug and drug-exipients obtained shown in Figure 5(a) and Figure 5 (b) respectively.

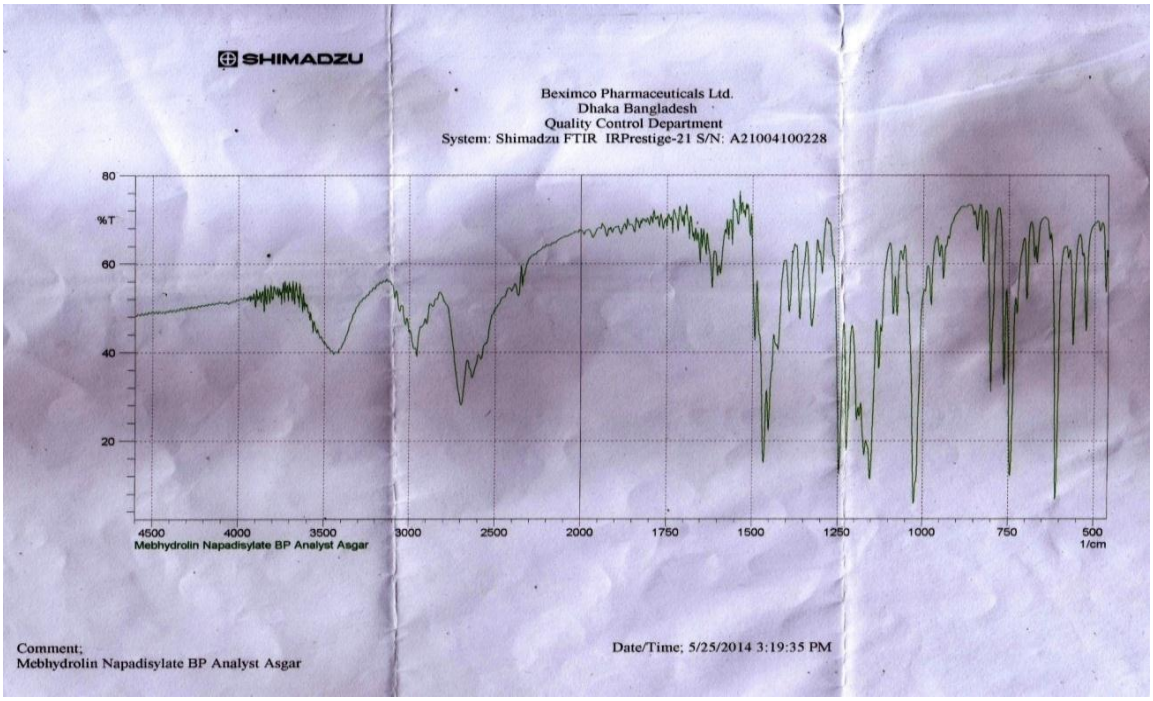


**Figure 5(a): IR spectrum of Pure Mebhydrolin Napadisylate**

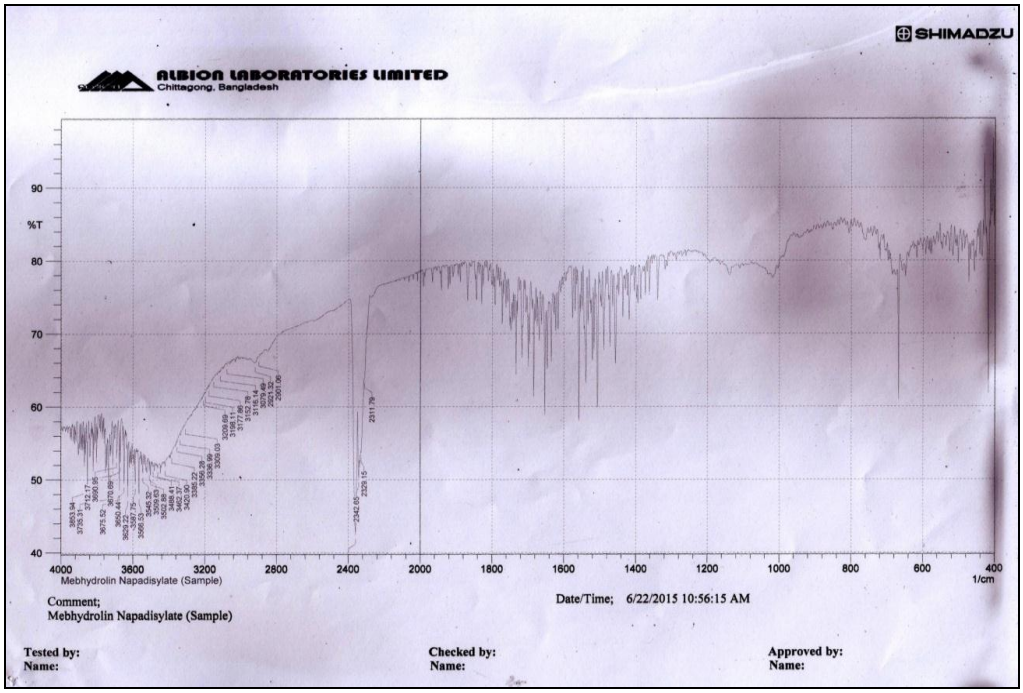


**Figure 5 (b): IR spectrum of Mebhydrolin Napadisylate – Exipients**

## CONCLUSION

The present study was aimed at developing an oral gastro retentive floating system of Mebhydrolin Napadisylate for an effective and safe therapy by using different polymer ratios of HPMC K4M and HPMC K 100LV. The addition of gel forming polymers and gas generating agent sodium bi carbonate and citric acid were essential to achieve the *in vitro*

buoyancy. The drug release from the tablets was sufficiently sustained due to the presence of the polymers. Mebhydrolin Napadisylate floating tablet drug delivery system showed improved in vitro bioavailability and extended drug release which may favor the reduced dose frequency and patient compliance. From the results obtained, it was concluded that the formulation F3 (polymer ratio 1:1) is the best formulation as the extent of drug release was found to be around 90%. This batch also showed immediate floatation and longer floating time. The in vitro release model of this formulation complies with zero order kinetics. Since the formulation showed sufficient release for prolonged period, the dose can be reduced and possible incomplete absorption of the drug can be avoided.

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