Journal of Pharmaceutical Advanced Research

(An International Multidisciplinary Peer Review Open Access monthly Journal)

Available online at: www.jparonline.com

RESEARCH ARTICLE JPAR 2024

Formulation and Evaluation of Floating drug Delivery system of Mebeverine Hydrochloride

Sujan Neupane[1]* , Hemank K.C.[1] , Renuka Tamang[1] , Richa Tandulkar[1], Melina Thapa Magar[1] , Lalit Rawal[1], Ashish Thagunna[1], Sanjeev Gurung[1], Pramod Kharel[2]

[1]Valley College of Technical Sciences, Purbanchal University, Kathmandu, Nepal.
[2]National Academy for Medical Sciences, Kathmandu, Nepal.

Received: 22.04.2024 Revised: 10.05.2024 Accepted: 18.05.2024 Published: 30.05.2024

ABSTRACT: Background: Mebeverine HCl is an antispasmodic drug, which has poor bioavailability and hence undergoes first pass metabolism. **Aim:** The aim of the present work is to formulate and evaluate the floating tablet of Mebeverine HCl with a purpose of increment in bioavailability avoiding first pass metabolism. Thus, the drug shows local action in GIT. **Method:** Sodium bicarbonate and Citric acid were used as effervescent agent. Various polymers like HPMC, HPMC 15cps and Sodium alginate were employed during the formulation process. Pre-compression and post compression parameters were evaluated. **Results:** FTIR studies showed that there was no interaction between drug and polymers. Altogether, nine formulations were prepared. According to the data obtained from disintegration time, friability and drug release studies, the formulation containing HPMC 15 cps in formulation F9 showed disintegration time 9.18 ± 0.144 s, 0.513 ± 0.12 % friability with % drug release of 97.561 % at the end of 8 h with the Floating time of 22 s. **Conclusion:** The optimized Mebeverine Hydrochloride floating tablet formulation, F9 contains 3 % of HPMC 15 cps.

Corresponding author:
Mr. Sujan Neupane
Assistant Professor
Valley College of Technical Sciences,
Purbanchal University, Kathmandu, Nepal.
Tel: +977- 9864040484
E. Mail ID: hemankkc322@gmail.com
sujan.neupane93@gmail.com

Keywords: Mebeverine HCl, floating tablets, HPMC 15 cps, increment in bioavailability, floating lag time.

INTRODUCTION:

Conventional controlled drug release systems such as tablets, capsules, pills, etc. do not offer an ideal drug release profile from a pharmacokinetic point of view, mainly high- toxicity drugs with a narrow therapeutic range. This type of system is unable to ensure the drug stability, which can affect the molecule bioavailability over the application. To overcome this problem, researchers are working on the development of new release systems that are able to protect the drug against premature degradation or inactivation as well as to deliver into the specific sites of action, thus maximizing the impact on the effective therapy in several treatments [1].

A route of drug administration is the path by which a drug is taken into the body. The various routes of administration are categorized as oral, sublingual, rectum, intravascular, intramuscular, subcutaneous and inhalation [2]. Oral delivery of drugs is the most preferable route of drug delivery due to the ease of administration, low cost of therapy, patient compliance and flexibility in formulation etc. [3].

Around 60 % of established small molecule drug products available commercially are administered *via* oral route. In this route, the drug is placed in the mouth and swallowed. It is also called per oral route. [4].

Floating drug delivery system is a type of hydrodynamically balanced system. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of the drug, the residual system is emptied from the stomach. This results in an increased gastric residence time and a better control of fluctuation in plasma drug concentration. Hydrodynamically balanced system can remain in the stomach for long periods and release the drug over a prolonged period of time [5].

To formulate a successful gastro-retentive drug delivery system, several techniques are currently used such as floating drug delivery systems, low-density systems, raft systems incorporating alginate gel, bioadhesive or mucoadhesive systems, high density systems, super porous hydrogel and magnetic systems. Among which the floating dosage forms have been most commonly used [6].

Floating drug delivery systems have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time [7].

FDDS offer various potential advantages for drugs, which have local gastric effects. For example; Furosemide are mainly absorbed in the stomach and have an absorption window in the upper part of the small intestine. PABA exhibits low solubility at high pH value and is unstable in the small intestine of colon [8].

Mebeverine is a cholinergic muscarinic antagonist, and acts directly on the smooth muscles of the intestine. It has poor oral bioavailability; it suffers extensive first pass metabolism through the action esterase in the blood plasma. Because of its mechanism of action and *in-vivo* degradation, traditional Mebeverine-HCl formulations do not provide immediate relief of symptoms and typically show activity 2 h, after administration [9].

Mebeverine HCl being an antispasmodic drug should act locally in the gastro-intestinal tract for a longer duration of action. Mebeverine HCl is absorbed from the GI tract, thus shows local action in the gastrointestinal tract. This drug has poor bioavailability so undergoes first pass metabolism. The basic goal of designing a floating drug delivery system is to reduce the fluctuations in the drug plasma concentration for a prolonged time period, better patient tolerance, reduce dosing frequency and dose, increase effectiveness and efficacy with minimum side effects of the drug. The drug is dispersed in swellable hydrophilic polymer to sustain the drug release.

Floating drug delivery system of Mebeverine HCl facilitates the buoyancy of the drug in the gastric pH and acid. The longer the buoyancy of the drug in gastric fluid, the more the effect of the drug can be observed. The release rate of the drug formulation can be known from the *in vitro* dissolution testing in the simulated gastric fluid. The reason behind making the drug float in 0.1N HCl is having the pH similar to that of pH of the stomach. The drug retains buoyancy in the stomach, which results in an increase in bioavailability. This ultimately extends the release of drugs within the stomach and hence reduces dosing frequency.

Mebeverine HCl is not absorbed completely from GIT. Therefore, there is a need to develop floating tablets of Mebeverine HCl to increase the gastric residence time and hence increase drug absorption.

MATERIALS AND METHOD:

Mebeverine HCl was received as a gift sample from Chemi Drug Industries Private Limited, Thankot, Kathmandu. Sodium Alginate, Mannitol, Sodium bicarbonate, citric acid, Ethyl cellulose, Talc, Magnesium stearate, Lactose were of analytical grades.

Pre-formulation Studies [10-12]:

***Color and Appearance*:**

The sample was observed visually for color and appearance.

***Melting point*:**

The melting point of Mebeverine HCl is determined by introducing a tiny amount of drug into a small capillary tube attaching this to the stem of a thermometer centered in a heating bath, heating the bath slowly and observing the temperature at which melting begins and is complete.

***Solubility*:**

The maximum amount of a substance that will dissolve in a given amount of solvent at a specified temperature is known as solubility. The standard solubility data is given in Table 1.

Table 1. Standard table for solubility studies.

Descriptive terms	Relative amounts of solvents to dissolve 1 part of solute
Very soluble	less than 1
Freely soluble	1-10
Soluble	10-30
Sparingly soluble	30-100
Slightly soluble	100-1000
Very slightly soluble	1000-10000
Insoluble or practically insoluble	more than 10000

***Drug/Polymer interaction by FTIR analysis*:**

FTIR study was performed to verify pure drug and polymer interaction. The study of polymer drug interaction between Mebeverine with HPMC, HPMC 15 cps, and Sodium alginate were performed by FTIR. It was performed by KBr method. The pure drug powder with KBr and pellet was prepared by high pressure to 100 kg/cm for 2 min. The obtained powder was analyzed in FTIR. KBr was obtained initially before the analysis of test samples. The procedure was repeated for the analysis of drug and excipients.

Development of analytical method:

Analytical methods such as UV/VIS spectrophotometric methods are evaluated for the estimation of Mebeverine HCl in formulations.

***Preparation of stock solutions*:**

Standard Mebeverine HCl 10 mg was weighed and transformed to 100 ml volumetric flask and dissolved in 25 ml of 0.1N HCl. The flask was shaken and volume was made up to the mark with 0.1N HCl to give a solution containing 100 µg/ml.

***Determination of Absorption Maxima (λ_{max}) of Mebeverine HCl*:**

From the standard stock solution of Mebeverine, appropriate aliquots 1.5, 2.5, 2.5, 2.5, and 3.0 ml were pipetted out in 20, 50, 25, 20, and 20 ml volumetric flasks respectively. Dilutions are made with 0.1N HCl to obtain a working standard solution of concentrations from 5 to 15 µg/ml. Absorbance for these solutions are measured by using the UV-Visible spectrophotometer at wave length region of 200 to 400 nm.

Standard calibration curve for the Mebeverine HCl:

Appropriate volumes of aliquots from standard Mebeverine stock solution were transferred to different volumetric flasks. The volume was adjusted to the mark with 0.1N HCl to obtain concentrations of 5, 7.5, 10, 12.5, and 15 µg/ml. The 0.1N HCl as a blank solution against each solution, then absorbance value is measured at λ_{max} 220 nm. From the absorbance value, regression equation and correlation coefficient (r^2) can be determined.

Pre-compression parameters [13,14]:

***Bulk Density*:**

The pure drug powder was weighed and poured into a measuring cylinder, the initial (bulk) volume (Vb) was noted. The bulk density is the mass of the powder per unit volume of powder. It is expressed in g/ml and is given by equation 1.

Bulk density (Db) =W/Vb ....(1)

Where, W = mass of the powder and Vb = bulk volume of the powder.

***Tapped Density*:**

Volume measured by tapping the powder for 50 times using a bulk density apparatus was the tapped volume. The final tapped volume was noted and various flow properties are calculated. It is expressed in g/ml and is given by equation 2.

Tapped volume (Dt) = W/Vt ....(2)

Where, W = mass of the powder and Vt = tapped volume of the powder.

Angle of repose:

Angle of repose was determined by the funnel method. The powder was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. The diameter (d) of the base of the pile was measured and radius(r) was calculated. Therefore, the angle of repose was calculated by using the equation 3 and the value was correlated with the data given in Table 3. The frictional pressure is an unfastened powder or granules can be measured by using angle of repose.

$\tan(\theta) = h/r$

$(\theta) = \tan^{-1}(h/r)$ ....(3)

Where, h is the height of the pile and r is the radius of the base of the pile.

Hausner's ratio:

Hausner's ratio is the number that is correlated to the flow ability of a powder. It is calculated by the following formula.

Hausner's ratio = Dt/Db …(4)

Where, Dt is tapped density and Db is bulk density.

Compressibility index / Carr's Index:

The compressibility index is determined by using the following equation.

Carr's Index (%) = [(Dt-Db)/Dt] × 100 …(5)

The obtained Hausner's ratio and Compressibility index values were correlated with the data given in Table 3 and Flow property was determined.

Table 2. Angle of repose and their effect in flow properties.

Angle of Repose (in ^{0})	Flow properties
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Table 3. Effects of Hausner's ratio and Compressibility index on flow properties.

Hausner's ratio	Flow property	Compressibility index (%)
1.00-1.11	Excellent	0-10
1.12-1.18	Good	11-15
1.19-1.25	Fair	16-20
1.26-1.34	Passable	21-25
1.35-1.45	Poor	26-31
1.46-1.59	Very poor	32-37

Preparation of floating tablet of Mebeverine HCl [15]:

A direct compression technique is used for the preparation of a floating drug delivery system of Mebeverine HCl. Nine batches (F1 to F9) tablets are prepared from active drug Mebeverine HCl along with different concentrations of excipients. Initially the drug, Mebeverine HCl and different excipients such as HPMC, HPMC 15 cps, sodium alginate, mannitol, sodium bicarbonate, citric acid, ethyl cellulose, talc, magnesium stearate and lactose are individually screened through sieve #40. The required amount of active drug, polymer and other additives are mixed homogeneously. At last Magnesium stearate is then added in the mixture. The mixtures are compressed into tablets using a 10-station rotating tablet-punching machine.

Post-compression Evaluation [11,15-17]:

***Hardness*:**

The hardness of a tablet is determined using the Monsanto hardness tester. The tester is placed across the diameter in between the spindle and the anvil. The knob is adjusted to hold the tablet in position. The reading of the pointer is adjusted to zero; the pressure is increased slowly to break the tablet. Hardness factor, the average of the several determinations is recorded.

***Thickness*:**

The thickness of a tablet is determined by using Vernier calipers. The tablets are placed between two arms of the Vernier caliper and measure the thickness of the tablets. Three tablets were used and the average value was calculated.

***Weight Variation*:**

Ten tablets were selected randomly from each batch and weighed individually using electronic balance to check for weight variation.

Table 5. Limit for weight variation (I.P.).

Average weight of a tablet	Percentage deviation (%)
80 mg or less	10
more than 80 mg and less than 250 mg	7.5
250 mg or more	5

***Friability*:**

Roche friability is used to measure the friability of the tablets. It is made to rotate at the rate of 25 rpm. About 10 tablets are weighed collectively and placed in the chamber of the friabilator. In the friabilator the tablets are exposed to rolling, resulting from free fall of tablets within the chamber of the friabilator. After 100 rotations (4 min), the tablets are taken out from the friabilator and intact tablets are dedusted and again weighed collectively. Percentage friability is determined by using the following formula.

Friability = [(W1-W2)/ W1]×100

Where, W1 = weight of the tablets before test and W2 = weight of the tablets after test.

***In vitro buoyancy studies*:**

The *in vitro* buoyancy was determined by floating lag time and total floating time. The tablets were placed in a 100 ml beaker containing 0.1N HCl. The time required for the tablets to raise the surface and float is determined as floating lag time and the duration of the tablet consistently floating on the dissolution medium was determined as total floating time.

Table 4. Formulation of floating tablets of Mebeverine HCl by direct compression method.

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Mebeverine HCl	135.496	135.496	135.496	135.496	135.496	135.496	135.496	135.496	135.496
Sodium alginate	3.5	7	10.5	-	-	-	-	-	-
HPMC	-	-	-	3.5	7	10.5	-	-	-
HPMC 15cps	-	-	-	-	-	-	3.5	7	10.5
Sodium bicarbonate	52.5	52.5	52.5	52.5	52.5	52.5	52.5	52.5	52.5
Mannitol	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Citric acid	35	35	35	35	35	35	35	35	35
Ethyl cellulose	70	70	70	70	70	70	70	70	70
Talc	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5
Magnesium Stearate	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5
Lactose	22.004	18.504	15.004	22.004	18.504	15.004	22.004	18.504	15.004
Total	350	350	350	350	350	350	350	350	350

***All ingredients are measured in mg.**

***Disintegration Studies*:**

The disintegration test apparatus is used to conduct the disintegration study. The test was carried out on 3 tablets in each batch formulation using disintegration media, 900 ml 0.1N HCl at temperature 37± 0.5 ºC. The time (min) was calculated for the complete disintegration of the tablets, so that there was no mass remaining in the baskets of disintegration apparatus.

***In vitro Dissolution Studies*:**

In vitro drug release studies were carried out by using USP Dissolution Testing Apparatus II (Paddle type). The temperature of the dissolution flask was maintained at 37± 0.5 ºC and filled 900 ml 0.1N HCl in the vessels. The apparatus was allowed to run for 8 h at 50 rpm. About 5 ml sample solution was withdrawn after every 1 h using a pipette. The amount of sample withdrawn was replacing equal volume of buffer. All samples were suitably diluted and analyzed by double beam UV-Visible Spectrophotometer at 220 nm to determine the amount of drug content.

***Assay*:**

Triturating 20 tablets determined the drug content in each formulation, and powder equivalent to average weight was added in 100 ml of 0.1N HCl, followed by continuous stirring. The solution was filtered through filter paper, diluted suitably, and the absorbance of the resultant solution was measured by using the UV-Visible Spectrophotometer at 220 nm using 0.1N HCl as blank.

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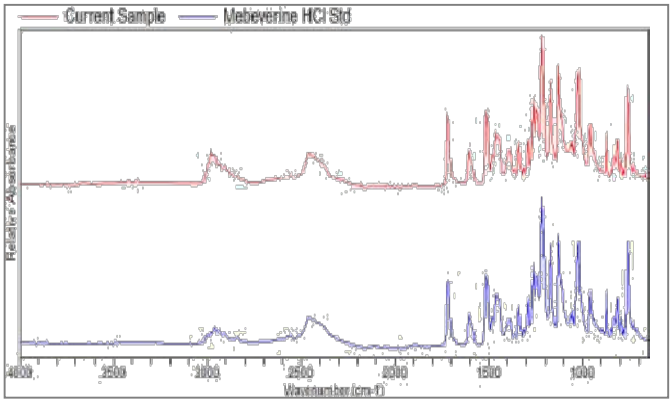

Fig 1. FTIR of pure drug (Mebeverine HCl).

RESULTS:

Pre-formulation studies:

The drug was almost white crystalline powder. The melting point of Mebeverine HCl was found to be 131.6 ºC.

Mebeverine HCl was very soluble in water, freely soluble in ethanol and insoluble in ether. From the FTIR data (Fig 1 to 4) it was revealed that there was no interaction between the pure drug and excipients in the physical mixture.

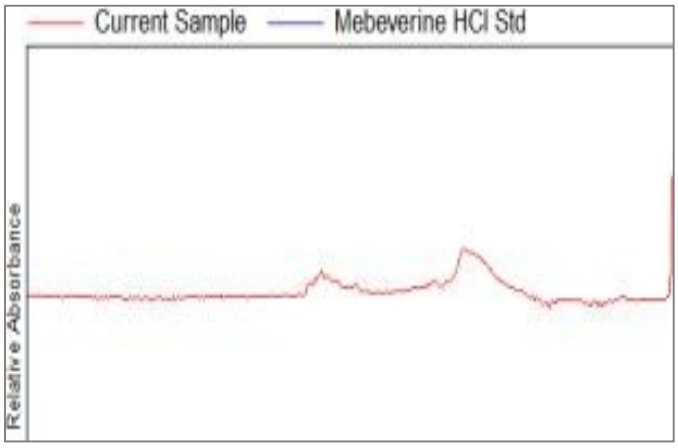

Fig 2. FTIR spectrum of Mebeverine HCl and HPMC.

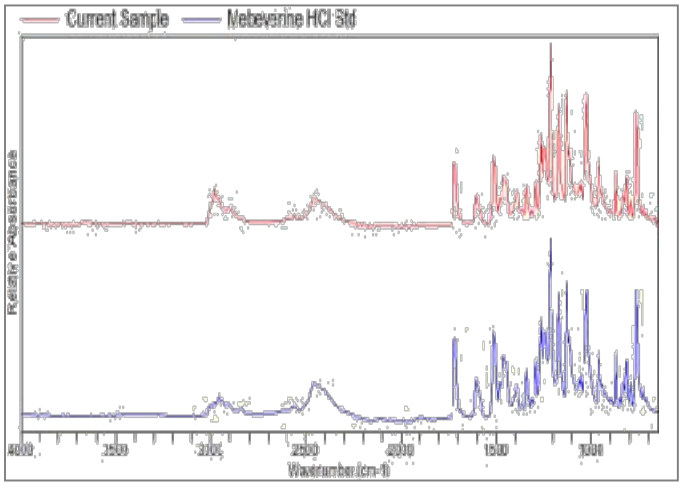

Fig 3. FTIR spectrum of Mebeverine HCl and Sodium Alginate.

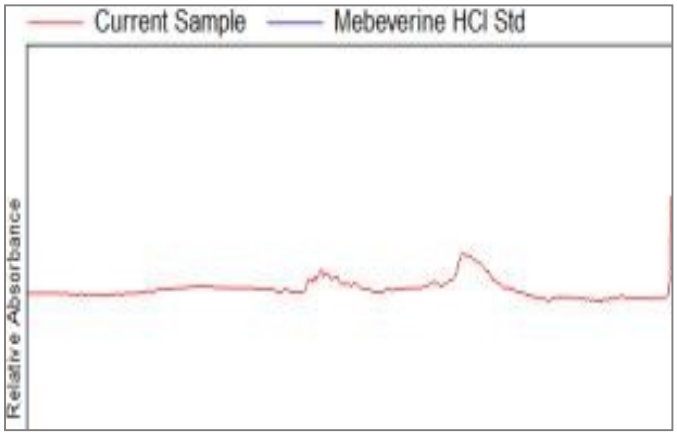

Fig 4. FTIR Spectrum of Mebeverine HCl with HPMC 15 cps.

Calibration curve of pure drug:

A spectrum of the working standards was obtained by scanning from 200 to 400 nm by UV-Visible spectrophotometer against the reagent blank to fix absorption maxima. The λ_{max} was found to be 220 nm. The linearity range obtained was from 5 to 15 µg/ml and the slope was found to be 0.029.

Table 6. Data for calibration curve of Mebeverine HCl in 0.1N HCl at 220 nm.

Concentration (µg/ml)	Absorbance
5	0.145
7.5	0.226
10	0.298
12.5	0.371
15	0.436

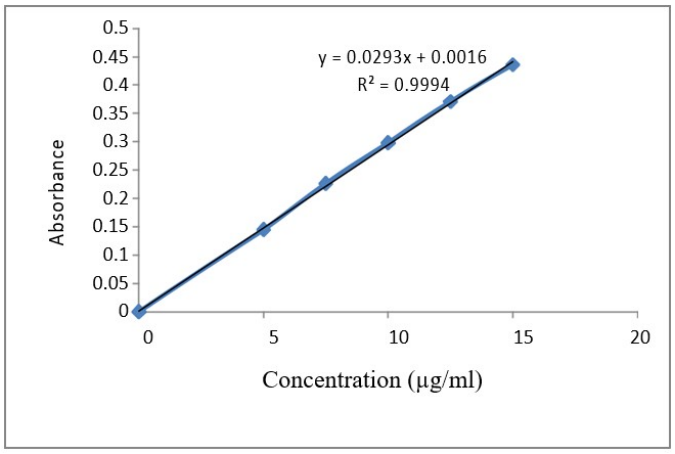

Fig 5. Standard calibration curve of Mebeverine HCl in 0.1N HCl at 220 nm.

Pre-compression evaluation studies:

Table 7. Bulk Density and Compressibility index of various formulations.

FC	Bulk Density (g/ml)	Tapped Density (g/ml)	Hausner's Ratio	CI (%)
F1	0.332±0.01	0.421±0.02	1.272±0.15	28.1±1.7
F2	0.383±0.001	0.578±0.007	1.508±0.01	33.7±0.6
F3	0.329±0.02	0.487±0.02	1.483±0.06	32.5±2.8
F4	0.327±0.05	0.540±0.07	1.680±0.36	32.1±0.5
F5	0.33±0.01	0.478±0.02	1.44±0.05	30.8±2.8
F6	0.386±0.06	0.554±0.05	1.364±0.54	34.87±9.7
F7	0.377±0.001	0.495±0.04	1.311±0.12	27.56±7.5
F8	0.328±0.01	0.477±0.02	1.450±0.05	30.97±2.8
F9	0.309±0.009	0.493±0.02	1.593±0.06	37.19±2.5

Each data is presented as Mean ± standard deviation (n=3). FC – Formulation Code, CI – Compressibility index.

The above table shows that bulk density ranges from 0.309 ± 0.009 to 0.386 ± 0.06 g/ml and tapped density ranges from 0.421 ± 0.02 to 0.578 ± 0.007 g/ml. The compressibility index value ranges from 27.56 ± 7.5 to 37.19 ± 2.5 and Hausner's ratio ranges from 1.272 ± 0.15 to 1.680 ± 0.36 %.

Table 8. Angle of Repose of various formulations.

Formulations	Angle of repose (º)
F1	47.22 ± 1.40
F2	47.05 ± 2.05
F3	38.25 ± 4.94
F4	42.21 ± 3.92
F5	41.33 ± 2.30
F6	49.14 ± 1.74
F7	43.95 ± 2.03
F8	47.56 ± 5.60
F9	45.42 ± 1.24

Each data is presented as Mean ± standard deviation (n=3).

From the above table, the angle of repose of pre-compressed powders of Mebeverine HCl was in the ranges from 38.25 ± 4.94 to 49.14 ± 1.74 º.

Post compression evaluation:

All the tablet formulations were evaluated for various post compression parameters such as hardness, friability, thickness, weight variation, friability, *in vitro* dissolution studies and analysis of dissolution data, *in vitro* buoyancy test determination. All the formulations showed a total floating time of more than 8 h.

Tablet hardness of all batches was found to be in range of 3.5-4.16Kg/cm^2, thickness between 3.83 to 4.2 mm, friability between 0.316 to 0.63 %, tablet weight in the range of 349.8 ± 1.68 to 353.9 ± 1.6 mg. The disintegration time of all the formulations was recorded using disintegration apparatus.

The assay study showed that the percentage purity of drug was found to be 93.63 %.

DISCUSSION:

An attempt was made to formulate the floating tablet of Mebeverine HCl implementing direct compression technique with various ratios of different polymers. Pre-compression and post-compression parameters were evaluated as prescribed by the pharmacopoeias.

The FTIR spectrum of the drug was compared with frequencies of its standard functional groups, which were in the range indicating that Mebeverine HCl was of pure quality. FTIR spectrum obtained for the drug with

Table 9. Post compression evaluation of formulated floating tablets.

Formulations	Thickness (mm)	Hardness (kg/cm^3)	Friability (%w/w)	Weight variation (mg)	Floating Lag Time (s)	DT (min)
F1	3.83 ± 0.72	3.83 ± 0.28	0.443 ± 0.07	352.8 ± 3.37	112	11.98 ± 1.615
F2	4.36 0 ± 0.37	3.66 ± 0.28	0.506 ± 0.04	353.9 ± 1.96	108	12.35 ± 2.695
F3	4.06 ± 0.15	3.83 ± 0.28	0.52 ± 0.03	351.8 ± 2.97	93	10.86 ± 0.466
F4	4.83 ± 0.05	3.5 ± 0.5	0.316 ± 0.04	353.8 ± 2.69	84	13.44 ± 0.060
F5	4.13 ± 0.05	4.16 ± 0.28	0.346 ± 0.005	353.2 ± 4.77	71	12.26 ± 0.171
F6	4.86 ± 0.05	3.66 ± 0.57	0.503 ± 0.03	349.3 ± 1.25	63	10.71 ± 0.263
F7	4.26 ± 0.05	3.83 ± 0.28	0.463 ± 0.02	350.8 ± 2.20	58	10.89 ± 0.261
F8	4.23 ± 0.15	3.83 ± 0.28	0.63 ± 0.04	349.8 ± 1.68	45	10.69 ± 0.317
F9	4.23 ± 0.05	3.66 ± 0.28	0.513 ± 0.12	352.6 ± 2.36	22	9.18 ± 0.144

Each data is presented as Mean ± standard deviation (n=3). DT – Disintegration time.

Table 11. *In vitro* drug release study of formulated tablets (F1-F9).

Time (h)	Percentage drug release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	15.034	20.545	22.102	26.019	35.891	45.488	54.008	65.872	71.576
2	15.632	22.549	25.913	27.546	41.292	46.087	59.019	68.450	73.062
3	18.241	28.582	26.743	28.774	45.505	49.479	63.353	72.310	76.397
4	19.696	31.534	43	36.375	49.626	52.522	67.389	76.005	80.504
5	23.045	38.60	49.540	49.743	57.318	55.352	69.910	80.910	83.807
6	23.338	41.377	52.148	59.291	60.173	62.913	73.314	83.778	86.782
7	30.955	45.976	59.854	62.203	65.584	68.179	76.941	87.232	89.771
8	54.646	57.586	67.738	69.916	70.612	71.136	80.701	94.574	97.561

formulation excipients showed characteristic peaks of the drug at their respective wavelength with no major shifts indicating compatibility of drug with the used excipients. Standard solution of Mebeverine HCl was scanned and showed maximum absorbance at 220 nm in 0.1N HCl, with regression coefficient 0.999 and hence obeyed "Beer-Lambert's law". The pre-formulation study showed that the powder exhibits passable to poor flow properties.

The average percentage weight variation and friability of all the prepared formulations are within the prescribed Pharmacopoeial limit. The tablet hardness was found to be within the range of 3.5 to 4.16 Kg/cm^2, which showed that all the formulation has good mechanical strength. Floating lag time ranges from 22 to 112 s. *In vitro* dissolution study was done by using USP type II apparatus with 0.1N HCl (pH 1.2) as a dissolution medium that showed the % drug release of all the formulations out of which F9 showed 97.561 % at the end of 8 h. The percentage purity of the drug was found to be 93.63 %.

CONCLUSION:

Floating tablets of Mebeverine HCl were successfully prepared by direct compression technique using various concentrations of polymers. Sodium bicarbonate and citric acid were used as gas forming agents to float the tablets in the stomach. FTIR spectrum obtained for drug with formulation excipients showed characteristic peaks with no interaction between drug and polymers. Pre-compression and post-compression parameters were evaluated. Among all the formulations, it was observed that the formulation containing HPMC 15 cps in formulation F9, showed disintegration time 9.18±0.144 s, 0.513±0.12 % friability with the % drug release of 97.561 % at the end of 8 h with the FLT of 22 s which satisfied all the tablet evaluation parameters for floating tablet. From all the experimental data, it can be summarized that F9 is the optimized formulation containing 3 % of HPMC 15 cps.

ACKNOWLEDGEMENT:

The authors wishes to thank Valley College of Technical Sciences, Purbanchal University, Kathmandu, for

providing the all facilities to complete this research work.

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Conflict of Interest: None
Source of Funding: Nil
Paper Citation: Neupane S*, Hemank KC, Tamang R, Tandulkar R, Magar MT, Rawal L, Thagunna A, Gurung S, Kharel P. Formulation and Evaluation of Floating drug Delivery system of Mebeverine Hydrochloride. J Pharm Adv Res, 2024; 7(5): 2206-2214.