Research Article

Development and Evaluation of Indapamide Effervescent Floating Tablets Using Different HPMC Grade Polymers

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ABSTRACT

The objective of this research was to prepare a Gastroretentive drug delivery system of Indapamide. Quick GI transit could result in incomplete drug release from the drug delivery system above the absorption zone leading to decreased efficacy of the administered dose and thus less patient compliance. Floating matrix tablets containing 100 mg Indapamide were developed using different effervescent salts and polymer. The tablets were prepared by direct compression method, using polymers such as H HPMC K100M, HPMC E50 and HPMC K15M. Sodium bicarbonate and citric acid was incorporated as a gas- generating agent. Different tablet properties, floating lag time and floating time and in-vitro drug release for 12h in 0.1mol/l HCl at 37ºC were studied. The result of floating lag time indicates content of Sodium bicarbonate and Citric acid in the formulations causes decreased floating lag time. All the batches showed floating time more than 12 hours. It is also observed that formulation F7 containing lowpolymer shows better controlled release behavior.

Keywords: Indapamide, Floating matrix Tablets, Polymer.

INTRODUCTION

Oral delivery of drugs is the preferable route of drug delivery. Oral route is considered most natural, uncomplicated, convenient and safe due to its ease of administration, patient compliance and flexibility in the formulation and cost effective manufacturing process[1]. Many of the drug delivery systems, available in the market are oral drug delivery type systems[2]. Pharmaceutical products designed for oral delivery are mainly immediate release type or conventional drug delivery systems[3,4].

Effervescent Floating drug delivery system (FDDS)

The FDDS utilize matrices prepared with swellable polymers such as methocel, polysaccharides, effervescent components like NaHCO3, citric acid, and tartaric acid or chamvers containing a liquid that gasifies at body temperature. The optimal stoichiometric ratio of citric acid and NaHCO3 for gas generation is reported to be 0.76:1 CO_2 is released, causing the beads float in the stomach[5-7]**.** The matrices are fabricated so that upon contact with gastric fluid, CO_2 is liberated by acidity of gastric contents and is entrapped in the gellified hydrocolloid. This produces an upward motion of the dosage form and maintains its buoyancy. The CO_2 generating components may be intimately mixed within the tablet matrix to produce a single-layered tablet or a bilayered tablet may be compressed which contains the gas generating mechanism in one hydrocolloid containing layer and drug in the other layer formulated for the sustained release effect[8]. This concept has also been exploited for floating capsule systems[9].

Indapamide it is an orally active sulphonamide diuretic agent. Although some evidence appears to indicate that the antihypertensive action of indapamide is primarily a result of its diuretic activity, only a limited diuresis occurs with the usual antihypertensive doses of 2.5 mg daily. The *in vitro* and *in vivo* data propose that Indapamide may also reduce blood pressure by reducing vascular reactivity and peripheral vascular resistance. In mild to moderate hypertension this drug is as effective as thiazide diuretics and ß -adrenergic blocking agents in lowering blood pressure when used as the sole treatment[10].

The main purpose of the present research work was to formulate effervescent floating tablets of indapamide using different HPMC grade polymers and evaluate its quality and drug release profile as well to justify the formulation.

MATERIALS AND METHODS

Materials

Indapamide was procured from Dr Reddy's Laboratories Ltd., India. HPMC K100M, HPMC E50 and HPMC K15M were procured from Arvind Remedies Ltd, India. Sodium Bicarbonate and Citric Acid were procured from Merck Specialities Pvt. Ltd, India. Magnesium Stearate and Talc were obtained from Kerry laboratories, India. Microcrystalline Cellulose was procured from SD Fine Chem. Labs, India.

Determination of absorption maxima

A solution containing the concentration 10µg/ml drug was prepared in 0.1N HCL UV Spectrum was taken using double beam UV/VIS Spectrophotometer. The Solution was scanned in the range of 200-400nm.

Preparation calibration curve[11]

10mg Indapamide pure drug was dissolved in 10ml of methanol (stock solution 1) from stock solution 1ml of solution was taken and made up with 10ml of 0.1N HCL (100µg/ml). from this 1ml was taken and made up with 10ml of 0.1N HCL (10µg/ml). The above solution was subsequently diluted with 0.1N HCL to obtain series of dilutions containing 2, 4, 6, 8, 10 µg/ml of per ml of solution. The absorbance of the above dilutions was measured at 240 nm by using UV-Spetrophototmeter taking 0.1N HCL as blank. Then a graph was plotted by taking concentration on X-Axis and absorbance on Y-Axis which gives a straight line linearity of standard curve was assessed from the square of correlation coefficient ($R^{2)}$ Which determined by least-square linear regression analysis. The standard curve is based on the spectrophotometry. The maximum absorption was observed at 240 nm. Graphs of Indapamide was taken in 0.1N HCL (pH 1.2) Standard graph of Indapamide was plotted as per the procedure in experimental method and its linearity is shown in Figure 1. The standard graph of Indapamide showed good linearity with R^2 of 0.9993, which indicates that it obeys "Beer-Lamberts" law.

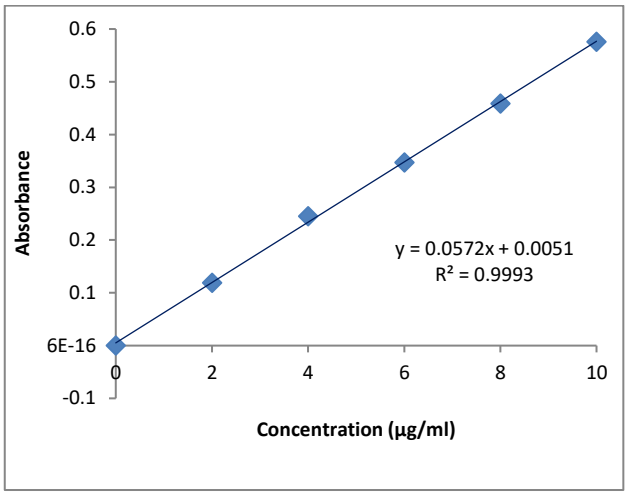

Figure 1: Standard graph of Indapamide in 0.1N HCL

Preparation of Indapamide Effervescent Tablets

Indapamide effervescent tablets were prepared by direct compression method using Tablet multi station compression machine (Lab Press Ltd., India). After dispensing required quantity of the drug and all other ingredients were individually passed through sieve no. ≠ 60 then all the ingredients were mixed thoroughly by triturating up to 15min.The powder mixture was lubricated with talc. The final blend was used to prepare the tablets with 6 mm punch in multi station compression machine[12]. Total 9 formulations were prepared and evaluated; the formulation chart was depicted in Table 1.

Table 1: Formulation composition for floating tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Indapamide	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
HPMC K100M	4	8	12	-	-	-	-	-	-
HPMC E50	-	-	-	4	8	12			
HPMC K15M	-	-	-	-	-	-	4	8	12
Sodium Bicarbonate	5	5	5	5	5	5	5	5	5
Citric Acid	3	3	3	3	3	3	3	3	3
Magnesium Stearate	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2
MCC	81.5	77.5	73.5	81.5	77.5	73.5	81.5	77.5	73.5
Total Weight	100	100	100	100	100	100	100	100	100

Preformulation parameters[13-15]

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per pharmacopoeia.

Angle of repose

The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is place on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The flow properties and corresponding angle of repose values were showed in Table 2. The radius (r) of the base of the conical pile was measured. The angle of repose was

calculated using the following formula:

$$\text{Tan } \theta = h/r$$

Tan θ=Angle of repose

h= Height of the cone,

r= radius of the cone base

Table 2: Flow Properties and Corresponding Angle of Repose

Flow Property	Angle of repose
Excellent	25-30
Good	31-35
Fair aid not to needed	36-40
Passable may hang up	41-45
Poor must agitate vibrate	46-55
Very poor	56-65
Very very poor	>66

Bulk density

Density is defined as weight per unit volume. Bulk density, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm^3. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. Bulk density is very important in size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment. 10gm powder blend was sieved and introduced into a dry 20ml cylinder, without compacting. The powder was carefully leveled without compacting and the unsettled apartment volume, Vo, was read.

The bulk density was calculated using the formula:

$$\text{Bulk density} = M/Vo$$

Where,

M= Weight of sample

Vo=Apparent volume of powder

Tapped density

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides 100 drops per minute and this was repeated until difference between succeeding measurement is less than 2% and then tapped volume, V Measured, to the nearest graduated unit. The tapped density was calculated, in gm per L, using the formula:

Tap= M/V

Where, Tap=Tapped density

M=Weight of sample

V=Tapped volume of powder

Measures of powder compressibility

The compressibility index (Carr's index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. As such, it is measures of the relative importance of inter particulate interactionscarr's index values as per USP were showed in Table 3. In a free- flowing powder, such interactions are generally less significant, and the bulk tapped densities will be closer in value. For poorer flowing materials, there are frequently greater inter particle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the compressibility index which is calculated using the following formulas:

$$\text{Carr's index} = [(\text{tap-b/tap}]\times 100$$

Where,

B=Bulk density

Tap= Tapped density

Table 3: Carr's index value (as per USP)

Compressibility Index (%)	Flow character
5-15	Excellent
12-16	Good
18-21	Fair to passable
22-35	Poor
33-38	Very poor
>40	Very very poor

Evaluation tests of post compression parameters for prepared Tablets[16, 17]

The designed compression tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

Weight variation test

To study the weight variation, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be satisfactory method of determining the drug content uniformity. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the following table and none deviate by more than twice the percentage. A pharmacopoeial specification for tablet weight variation was depicted in Table 4. The mean and deviation were determined. The percent deviation was calculated using the following formula.

$$\%\text{Deviation} = (\text{Individual weight- Average weight/Average weight}) \times 100$$

Table 4: Pharmacopoeial specifications for tablet weight variation

Avg. wt. of Tablet in mg (IP)	Avg. wt. of Tablet in mg (USP)	Max. % difference allowed
Less than 80	Less than 130	10
80-250	130-324	7.5
More than 250	More than 324	5

Hardness

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. For each formulation, the hardness of three tablets was determined using Monsanto hardness tester and the average is calculated and presented with deviation.

Thickness

Tablet thickness is an important characteristic in reproducing appearance. Tablet thickness is an important characteristic in reproducing appearance. Average thickness for core and coated tablets is calculated and presented with deviation.

Friability

It is measured of mechanical strength of tablets. Roche friabilator was used to determine the friability by following procedure. Pre weighed tablets were placed in the friabilator. The tablets were rotated at 25 rpm for 4 minutes (100 rotations). At the end of test, the tablets were re-weighed, and loss in the weight of tablet is the measure of friability and is expressed in percentage as

$$\% \text{ Friability} = [(W1-W2)/W1]\times 100$$

Where,

W1=Initial weight of tablets

W2=Weight of the tablets after testing

Determination of drug content

Both compression-coated tablets of were tested for their drug content. Ten tablets were finely powdered quantities of the powder equivalent to one tablet weight of Indapamide were accurately weighed, transferred to a 100ml volumetric flask containing 50ml water and were allowed to stand to ensure complete solubility of the drug. The mixture was made up to volume with water. The solution was suitably and the absorption was determined by UV-Visible spectrophotometer. The drug concentration was calculated from the calibration curve.

***In vitro* buoyancy studies**

The *in vitro* buoyancy was determined by floating lag time, and total floating time. (As per the method described by Rosa et al) the tablets were placed in a 100ml beaker containing 0.1N HCL. The time required for the tablet to rise to the surface and float was determined as floating lag time (FLT) and duration of time the tablet constantly floats on the dissolution medium was noted as total floating time respectively (TFT)[18].

***In vitro* drug release studies**

Dissolution parameters

Apparatus	:	USP-II, Paddle method
Dissolution medium	:	0.1N HCL
RPM	:	50
Sampling intervals (hrs)	:	0,0.5,1,2,3,4,5,6,7,8,9,10, 11 and 12 h.
Temperature	:	37±0.5˚c

As the preparation was for floating drug release given through oral route of administration, different receptors fluids are used for evaluation the dissolution profile.

Procedure

900ml of 0.1 N HCL was placed in vessel and the USP apparatus-II (Paddle method) was assembled. The medium was allowed to equilibrate to temp of 37˚c±0.5˚c. Tablet was placed in the vessel and the vessel was covered the apparatus was operated for 24 hrs at 50rpm. At definite time intervals of 5 ml of the receptors fluid was continued from 0 to 24 hrs at 50rpm. At definite time intervals of 5 ml of the receptors fluid was withdrawn, filtered and again 5ml receptor fluid was replaced. Suitable dilutions were done with media and analysed by spectrophotometrically at 240 nm using UV-Spectrophotometer.

Application of release rate kinetics to dissolution data[19]

Various models were tested for explaining the kinetics of drug release. To analyse the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Kors meyer-peppas release model.

Zero order release rate kinetics

To study the zero-order release kinetics the release rate data are fitted to the following equation.

$$F=Ko\ t$$

Where, F is the drug release at time ”t”, and “Ko” is the zero order release rate constant. The plot of % drug release versus time is linear.

First order release rate kinetics

The release rate data are fitted to the following equation

$$Log(100-F)=kt$$

A plot of log cumulative percent of drug remaining to be released vs. Time is plotted then it gives first order release.

Higuchi release model

To study the Higuchi release kinetics, the release rate data

fitted to the following equation.

$$F=kt1/2$$

Where, 'k' is the Higuchi constant.

In Higuchi model, a plot of %drug release versus square root time is linear.

Korsmeyer and peppas release model

The mechanism of drug release was evaluated by plotting the log percentage of drug released versus log time according to Korsmeyer-Peppas equation. The exponent 'n' indicates the mechanism of drug release calculated through the slope of the straight line.

$$M_t/M_\infty=Kt^n$$

Where, $M_t/M_\infty$is fraction of drug released at time 't',k represents a constant, and 'n' is the diffusional exponent, which characterizes the type of release mechanism during the dissolution process. For non-Fickian release, the value of n fallas between 0.5 and 1.0; while in case of Fickian diffusion, n=0.5; for zero-order release (case II transport), n=1; and for supercase II transport, n>1. In this model, a plot of log (M_t/M_∞) versus log (time) is linear.

Drug – excipients compatibility studies

Fourier transform infrared (FTIR) Spectroscopy[20]

The compatibility between the pure drug and excipients was detected by FTIR Spectra obtained on Bruker FTIR Germany(alpha T). The solid powder directly place on yellow crystal which was made up of ZnSe. The spectra were recorded over the wavenumber of 4000cm^{-1} to 550cm^{-1}.

RESULTS AND DISCUSSION

Preformulation parameters of powder blend

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.45 ± 0.04to 0.57 ± 0.06 (gm/ml) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.53 ± 0.02to 0.66 ± 0.03showing the powder has good flow properties. The compressibility index of all the formulations was found to be below 16.07 which show that the powder has good flow properties. All the formulations have shown the Hausner's ratio ranging between 1.12 ± 0.01to 1.24 ± 0.01indicating the powder has good flow properties. The Pre-formulation parameters of blend results depicted in Table 4.

Table 4: Pre-formulation parameters of blend

Formulation Code	Angle of Repose	Bulk density (gm/mL)	Tapped density (gm/mL)	Carr's index (%)	Hausner's Ratio
F1	25.98 ± 0.45	0.47 ± 0.02	0.53 ± 0.02	11.32 ± 0.01	1.12 ± 0.02
F2	25.19 ± 0.95	0.45 ± 0.04	0.56 ± 0.04	16.07 ± 0.02	1.24 ± 0.01
F3	27.82 ± 0.61	0.52 ± 0.03	0.60 ± 0.06	13.33 ± 0.03	1.15 ± 0.02
F4	28.85± 0.56	0.55 ± 0.04	0.62 ± 0.04	11.29 ± 0.04	1.12 ± 0.03
F5	25.95 ± 0.49	0.47 ± 0.03	0.56 ± 0.05	12.50 ± 0.03	1.19 ± 0.01
F6	25.85 ± 0.94	0.56 ± 0.02	0.63 ± 0.02	11.11 ± 0.02	1.12 ± 0.01
F7	26.59 ± 0.89	0.49 ± 0.05	0.58 ± 0.01	15.51 ± 0.01	1.18 ± 0.02
F8	27.56 ± 0.84	0.57 ± 0.06	0.66 ± 0.03	13.63 ± 0.04	1.15 ± 0.03
F9	28.51 ± 0.98	0.50 ± 0.04	0.59 ± 0.04	15.25 ± 0.03	1.18 ± 0.04

Quality control parameters for tablets

The prepared 9 formulations were tested for weight variation, hardness, friability, thickness, drug content, floating time, total floating time and drug release studies and all the parameters such as weight variation, friability, hardness, thickness, and drug content were found to be within limits. The obtained results were showed in Table 5.

***In vitro* Dissolution**

The drug release rate from tablets was studied using the USP type II dissolution test apparatus. The dissolution medium was 500 ml of 0.1 N HCl at 50 rpm at a temperature of 37±0.5 ˚C. Samples of 5 ml were collected at different time intervals up to 12 hrs and has analyzed after appropriate dilution by using UV spectrophotometer at 240 nm. From the drug release results, it was observed that, formulation F7 (99.18%) showed fastest drug release by the end of 20th h. Formulation F1, F2, F3, F4, F5, F6, F8 and F9 showed the release upto 77.38%, 87.59%, 89.85%, 98.76%, 80.78%, 88.49%, 90.77% and 95.24% respectively at the end of 12 h. The results were depicted in Figure 2.

Table 5: Quality control parameters for compressed tablets

Formulation code	Average Weight (mg)	Hardness (kg/cm²)	Friability (%loss)	Thickness (mm)	Drug content (%)	Floating Lag time(Seconds)	Total floating time(Hours)
F1	98.57	4.3	0.12	3.21	97.49	59	11
F2	96.32	4.5	0.49	3.46	99.52	64	11
F3	99.78	5.1	0.53	3.19	98.19	15	12
F4	96.28	4.8	0.47	3.56	97.51	28	10
F5	99.14	4.7	0.25	3.42	99.55	39	12
F6	97.34	5.3	0.33	3.11	96.82	18	11
F7	99.67	4.0	0.15	3.85	99.32	12	12
F8	98.46	5.2	0.57	3.24	98.69	51	10
F9	99.15	4.5	0.60	3.63	97.80	38	9

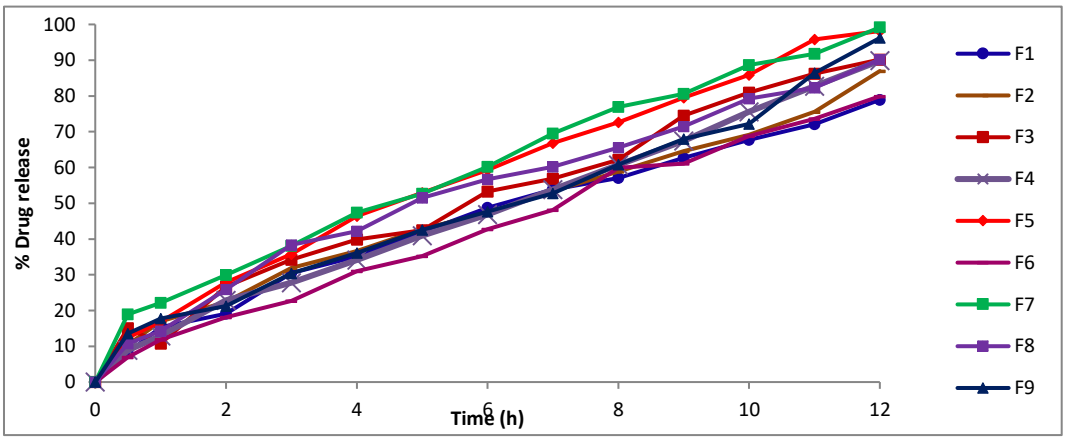

Figure 2: *In vitro* release of nine formulations (F1-F9)

From the dissolution data it was evident that the formulations prepared with HPMC K100M polymer were retarded the drug release more than 12 hours. Whereas the formulations prepared with higher concentration of HPMC E50retarded the drug release up to 12 hours. In lower concentrations the polymer was unable to retard the drug release.Whereas the formulations prepared with low concentration of HPMC K15M retarded the drug release up to 12 hours. In higher concentrations the polymer was unable to retard the drug release. Hence from the above dissolution data it was concluded that F7formulation was considered as optimized formulation because good drug release (99.18 %) in 12 hours.

Application of release rate kinetics to dissolution data for optimised formulation

The optimized formulation F7 was kept for release kinetics studies and the results obtained were showed in Table 6. From the above graphs it was evident that the formulation F7 was followed Higuchi release kinetics.

Table 6: Application kinetics for optimised formulation

Cumulative (%) release Q	Time (T)	Root (T)	LOG(%) Release	LOG (T)	LOG (%) Remain	Release Rate (Cumulative % Release / t)	1/CUM% Release	Peppas og Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
18.95	0.5	0.707	1.278	0.301	1.909	37.900	0.0528	-0.722	81.05	4.642	4.328	0.314
22.12	1	1.000	1.345	0.000	1.891	22.120	0.0452	-0.655	77.88	4.642	4.270	0.371
29.91	2	1.414	1.476	0.301	1.846	14.955	0.0334	-0.524	70.09	4.642	4.123	0.519
38.09	3	1.732	1.581	0.477	1.792	12.697	0.0263	-0.419	61.91	4.642	3.956	0.686
47.35	4	2.000	1.675	0.602	1.721	11.838	0.0211	-0.325	52.65	4.642	3.748	0.894
52.63	5	2.236	1.721	0.699	1.676	10.526	0.0190	-0.279	47.37	4.642	3.618	1.023
60.19	6	2.449	1.780	0.778	1.600	10.032	0.0166	-0.220	39.81	4.642	3.415	1.227
69.51	7	2.646	1.842	0.845	1.484	9.930	0.0144	-0.158	30.49	4.642	3.124	1.518
76.95	8	2.828	1.886	0.903	1.363	9.619	0.0130	-0.114	23.05	4.642	2.846	1.796
80.57	9	3.000	1.906	0.954	1.288	8.952	0.0124	-0.094	19.43	4.642	2.688	1.953
88.61	10	3.162	1.947	1.000	1.057	8.861	0.0113	-0.053	11.39	4.642	2.250	2.392
91.75	11	3.317	1.963	1.041	0.916	8.341	0.0109	-0.037	8.25	4.642	2.021	2.621
99.18	12	3.464	1.996	1.079	-0.086	8.265	0.0101	-0.004	0.82	4.642	0.936	3.706

Drug – Excipient compatibility study by FTIR:

The compatibility studies were performed using FTIR spectrophotometer. The characteristic absorption peaks of Indapamide pure drug and mixture of other excipients were obtained at different wave numbers. The characteristic peaks were observed aromatic -O-H stretching vibrations2340.26 cm^{-1}, C=O Stretching 1614.35 $cm^{-1}$and COO stretching 1477.24 cm^{-1} obtained in pure Indamide and with exicipients were used. The above results were indicating that there was no incompatibility between the drug and excipients used and the FTIR graph Showed in Figure 3.

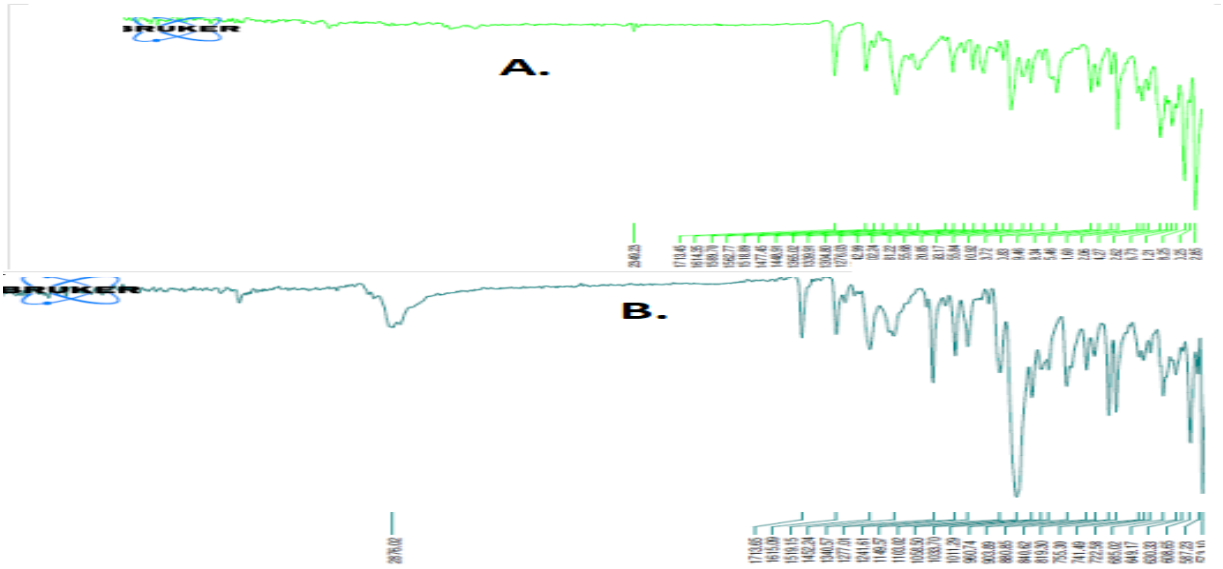

Figure 3: FTIR graphs for A. Pure drug and B. Optimized formulation

There was no disappearance of any characteristics peak in the FTIR spectrum of drug and the polymers used. This shows that there is no chemical interaction between the drug and the polymers used. The presence of peaks at the expected range confirms that the materials taken for the study are genuine and there were no possible interactions. Indapamide is also present in the physical mixture, which indicates that there is no interaction between drug and the polymers, which confirms the stability of the drug.

CONCLUSION

In the present research investigation, the floating matrix tablets of Indapamide were prepared by direct compression technique using HPMC grade polymer containing HPMC K100M, HPMC E50and HPMC K15M. Sodium bicarbonate and Citric acid were used as gas generating agent. Microcrystalline cellulose was used as diluents. Talc and magnesium stearate were used as glidant and lubricant respectively. All the batches showed floating time more than 12 hours which is quite significant for a floating matrix tablet. It is also observed that formulation F7 containing low polymers and gas generating agent shows better controlled release behavior. F7 formulation was considered as optimized with 99.18 % release of drug content. From the above graphs it was evident that the formulation F7 was followed Higuchi release kinetics.

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