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Research

Preparation And Evaluation Of Floating Tablets Of Clindamycin

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Abstract

The purpose of this research was to formulate and evaluate the Floating sustained release tablets of Clindamycin 150mg, an antibiotic drug. Clindamycin is a medication used to treat bacterial infections, including osteomyelitis (bone) or joint infections, pelvic inflammatory disease, strep throat, pneumonia, acute otitis media (middle ear infections), and endocarditis. The tablets are prepared by direct compression method. The formulations were optimized by incorporating varying composition of Eudragit RSPO, HPMC K 100, Chitosan and Micro crystalline cellulose as diluent, Sodium bicarbonate as floating agents, Magnesium stearate agent as lubricant. All the excipients are tested for compatibility with drug, which revealed that there was no physical and chemical interaction occurred. The Preformulation parameters such as bulk density, tapped density, compressibility index and Hausner's ratio were analyzed. The thickness, hardness, friability, weight variation, and drug content uniformity was evaluated for tablets. The effect of these variables on drug release also studied. The *In-Vitro* drug release studied were Performed in the USP dissolution apparatus-II (Paddle) using 0.1N HCL buffer as dissolution media at 50 rpm speed and temperature of 37oc ± 5ºC. the sampling was done at periodic time intervals of 0.5,1,2,3,4,5,6,7,8,9,10,11 and 12 hours and was replaced by equal volume of dissolution media after each withdrawal. The cumulative amount of drug release at different intervals is estimated using UV spectrophotometer. Based on the evaluation result the formulations F-3 containing Eudragit RSPO were selected as best formulation. The tablets were found to follow Kors mayer peppas release kinetics mechanism of drug release.

Keywords: Clindamycin, Eudragit RSPO, HPMC K 100, Chitosan and Floating tablets.

INTRODUCTION

Oral controlled release drug delivery have recently been of increasing interest in pharmaceutical field to achieve improved therapeutic advantages, such as ease of dosing administration, patient compliance and flexibility in formulation. Drugs that are easily absorbed from gastrointestinal tract (GIT) and have short half-lives are eliminated quickly from the systemic circulation. Frequent dosing of these drugs is required to achieve suitable therapeutic activity. After oral administration, such a drug delivery would be retained in the stomach and release

the drug in a controlled manner, so that the drug could be supplied continuously to its absorption sites in the gastrointestinal tract (GIT).[1] Prolonged gastric retention improves bioavailability, increases the duration of drug release, reduces drug waste, and improves the drug solubility that are less soluble in a high pH environment[2] Gastroretentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects. Gastroretentive dosage forms can remain in the gastric region for long periods and hence significantly prolong the gastric retention time (GRT) of drugs. Over the last few decades, several gastroretentive drug delivery approaches being designed and developed, including: high density (sinking) systems that is retained in the bottom of the stomach[3] , low density (floating) systems that causes buoyancy in gastric fluid[4,5,6], mucoadhesive systems that causes bioadhesion to stomach mucosa[7], unfoldable, extendible, or swellable systems which limits emptying of the dosage forms through the pyloric sphincter of stomach[8,9],superporous hydrogel systems[10] magnetic systems[11]etc. The current review deals with floating type gastroretentine drug delivery system.

Basic gastrointestinal tract physiology

The stomach is divided into 3 regions anatomically: fundus, body, and antrum pylorus. The proximal part is the fundus and the body acts as a reservoir for undigested material, where as the antrum is the main site for mixing motions and acts as a pump for gastric emptying by propelling actions. Gastric emptying occurs during fasting as well as fed states but the pattern of motility is distinct in the 2 states. During the fasting state an interdigestive series of electrical events take place, which cycle through both stomach and intestine every 2 to 3 hours. This is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), which is divided into following 4 phases.[12]

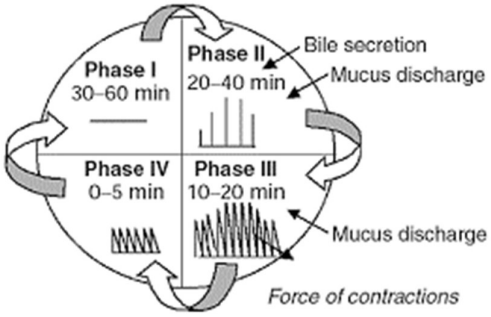

Fig 1: Schematic Representation of Interdigestive Motility

Phase I: This period lasts about 30 to 60 minutes with no contractions.
Phase II: This period consists of intermittent contractions that increase gradually in intensity as the phase progresses, and it lasts about 20 to 40 minutes. Gastric discharge of fluid and very small particles begins later in this phase.
Phase III: This is a short period of intense distal and proximal gastric contractions (4-5 contractions per minute) lasting about 10 to 20 minutes these contractions, also known as ‘‘house-keeper wave,’’ sweep gastric contents down the small Intestine.
Phase IV: This is a short transitory period of about 0 to 5 minutes, and the contractions dissipate between the last part of phase III and quiescence of phase

Need For Gastroretention

- Drugs that are absorbed from the proximal part of the gastrointestinal tract (GIT).
- Drugs that are less soluble or that degrade at the alkaline pH.
- Drugs that are absorbed due to variable gastric emptying time.
- Local or sustained drug delivery to the stomach and proximal small intestine to treat certain conditions.
- Particularly useful for the treatment of peptic ulcers caused by H.Pylori infections.[12]

Factors controlling gastric retention of dosage forms

There are several factors that can affect gastric emptying of an oral dosage form which include density, size and shape of dosage form, feeding state, biological factors such as age, gender, posture, body mass index, disease state etc.

Effect Of Dosage Form Size & Shape

Small size tablets are emptied from the stomach during the digestive phase while large size units are expelled during the house keeping waves found that floating unit with a diameter equal or less than 7.5 mm had larger gastric residence time (GRT) compared to nonfloating units but the GRT was similar for floating and non-floating units having a large diameter of 9.9 mm. They found that GRT of nonfloating units were much more variable and highly dependent on their size which are in the order of small < medium < large units. Moreover, in supine subjects, size influences GRT of floating and non- floating form. Tetrahedron and ring shaped devices have a better GRT as compared with other shapes.[13,14]

Density

The density of a dosage form also affects the gastric emptying rate and determines the location of the system in the stomach. Dosage forms having a density lower than the gastric contents can float to the surface, while high density systems sink to bottom of the stomach [16]. Both positions may isolate the dosage system from the pylorus. A density of < 1.0 gm/ cm3 is required to exhibit floating property.[15]

Gender, Posture & Age:

Generally females have slower gastric emptying rates than male. The effect of posture does not have any significant difference in the mean gastric retention time (GRT) for individuals in upright, ambulatory and supine state. In case of elderly persons, gastric emptying is slowed down.[16]

Effect of Food & Specific Gravity

To float FDDS in the stomach, the density of dosage form should be less than gastric content i.e.1.0 g/cm3. Since, the bulk density of a dosage form is not a sole measure to describe its buoyant capabilities because the magnitude of floating strength may vary as a function of time and gradually decrease after immersing dosage form into fluid as a result of development of its hydrodynamic equilibrium. Various studies have shown the intake of food as main determinant of gastric emptying rather than food. Presence of food is the most important factor effecting GRT than buoyancy. GRT is significantly increased under fed condition since onset of MMC is delayed. Studies show that GRT for both floating and non-floating single unit are shorter in fasted subjects (less than 2 hour), but significantly prolonged after meal (around 4 hour).[12]

Nature of Meal & Frequency of Food

Feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to fed state, to increase gastric emptying rate and prolonging the drug release. Diet rich in protein and fat can increase GRT by 4-10 hours.[12]

Type of Formulation

Multiple unit formulation show a more predictable release profile and insignificant impairing of performance due to failure of units, allow co-administration of units with different release profile or containing incompatible substances and permit a large margin of safety against dosage form failure compared with single unit dosage form.[13]

Future Potential:

Floating dosage form offers various future potential as evident from several recent publications. The reduced fluctuations in the plasma level of drug results from delayed gastric emptying. Drugs that have poor bioavailibility because of their limited absorption to the upper gastrointestinal tract can be delivered efficiently thereby maximizing their absorption and improving their absolute bioavalability.

Buoyant delivery system considered as a beneficial strategy for the treatment of gastric and duodenal cancers.

- The floating concept can also be utilized in the development of various anti-reflux formulations.
- Developing a controlled release system for the drugs, which are potential to treat the Parkinson's disease.
- To explore the eradication of Halico-bector pylori by using the narrow spectrum antibodies.[14]

MATERIALS AND METHODS

Clindamycin-Procured from Aurobindo Pharma, Hyderabad. Provided by SURA LABS, Dilsukhnagar, Hyderabad., Eudragit RSPO-Degussa India Ltd. (Mumbai, India), HPMC K 100 Arvind Remedies Ltd, Tamil nadu, India,Chitosan-Merck Specialities Pvt Ltd, Mumbai, India,Citric acid-Laser Chemicals, Ahmedabad, India, Sodium bicarbonate-Merck Specialities Pvt Ltd, Mumbai, India, Micro crystalline cellulose-Merck Specialities Pvt Ltd, Mumbai, India, Magnesium Stearate-Apex Chemicals, Ahmedabad, India, Talc-S.D. Fine Chem, Mumbai, India.

METHODOLOGY

Analytical method development
Characterization of Clindamycin
Organoleptic properties
Take a small quantity of sample and spread it on the white paper and examine it visually for color, odour and texture.

Determination of Clindamycin Melting point

The melting point of Clindamycin was determined by capillary tube method according to the USP. A sufficient quantity of Clindamycin powder was introduced into the capillary tube to give a compact column of 4-6 mm in height. The tube was introduced in electrical melting point apparatus and the temperature was raised. The melting point was recorded, which is the temperature at which the last solid particle of Clindamycin in the tube passed into liquid phase**.**

Determination of Clindamycin Solubility
Determination of solubility of drug by visual observation. An excess quantity of Clindamycin was taken separately and adds in 10 ml of different solutions. These solutions were shaken well for few minutes. Then the solubility was observed and observations are shown in the Table.

Determination of absorption maxima
A solution containing the concentration 10 µg/ 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 – 400 nm.

Preparation calibration curve
10mg Clindamycin pure drug was dissolved in 10ml of methanol (stock solution1) from stock solution 1ml of solution was taken and made up with10ml of 0.1N HCL (100µg/ml). From this 1ml was taken and made up with 10 ml of 0.1N HCL (10µg/ml). The above solution was subsequently diluted with 0.1N HCL to obtain series of dilutions Containing 5, 10, 15, 20, 25µg /ml of per ml of solution. The absorbance of the above dilutions was measured at 215 nm by using UV-Spectrophotometer 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.

Preformulation parameters
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 placed 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 radius (r) of the base of the conical pile was measured. The angle of repose was calculated using the following formula:

$\tan \theta = h / r$ $\tan \theta$ = Angle of repose
h = Height of the cone ,
r = Radius of the cone base

Table 1: Angle of Repose values (as per USP)

Angle of Repose	Nature of Flow
<25	Excellent
25-30	Good

30-40	Passable
>40	Very poor

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 the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment. 10 gm powder blend was sieved and introduced into a dry 20 ml cylinder, without compacting. The powder was carefully leveled without compacting and the unsettled apparent volume, Vo, was read.
The bulk density was calculated using the formula:
Bulk Density = M / V_o
Where, M = weight of sample
V_o = 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 interparticulate interactions. In a free- flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value.

For poorer flowing materials, there are frequently greater interparticle 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:
Carr's Index = [(tap - b) / tap] × 100
Where, b = Bulk Density
Tap = Tapped Density

Table 2: Carr's index value (as per USP)

Carr's index	Properties
5 – 15	Excellent
12 – 16	Good
18 – 21	Fair to Passable
2 – 35	Poor
33 – 38	Very Poor
>40	Very Very Poor

Formulation development of floating Tablets
Procedure for direct compression method:

1) Drug and all other ingredients were individually passed through sieve no ≠ 60.
2) All the ingredients were mixed thoroughly by triturating up to 15 min.
3) The powder mixture was lubricated with talc.
4) The tablets were prepared by using direct compression method by using 10mm punch.

Formulation of tablets

Table 3: Formulation composition for Floating tablets

INGREDIENTS (MG)	FORMULATION CODE								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Clindamycin	150	150	150	150	150	150	150	150	150
Eudragit RSPO	50	100	150	-	-	-	-	-	-
HPMC K 100	-	-	-	50	100	150	-	-	-
Chitosan	-	-	-	-	-	-	50	100	150
Citric acid	15	15	15	15	15	15	15	15	15
Sodium bicarbonate	20	20	20	20	20	20	20	20	20
Micro crystalline cellulose	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Magnesium Stearate	8	8	8	8	8	8	8	8	8
Talc	9	9	9	9	9	9	9	9	9
Total Weight	400	400	400	400	400	400	400	400	400

All the quantities were in mg

RESULT AND DISCUSSION

Organoleptic properties

Table 4: Organoleptic properties

S NO.	Properties	Results
1	State	Solid
2	Colour	White
3	Odour	Odourless
4	Melting point	141-143°C

Solubility studies

Table 5: Solubility studies of drug in different solvents

S NO.	Solvents	Solubility of Clindamycin
1	Ethanol	Slightly soluble
2	DMSO	Sparingly soluble
3	Dimethyl formamide.	Freely soluble
4	Methanol	Freely soluble
5	Water	Freely soluble
7	0.1 N HCl	Freely soluble

Analytical Method
Determination of absorption maxima
The standard curve is based on the spectrophotometer. The maximum absorption was observed at 215nm.

Calibration curve
Graphs of Clindamycin was taken in 0.1N HCL (pH 1.2)

Table 6: Observations for graph of Clindamycin in 0.1N HCL

Conc [µg/mL]	Abs
0	0
5	0.129
10	0.241
15	0.364
20	0.472

25	0.589

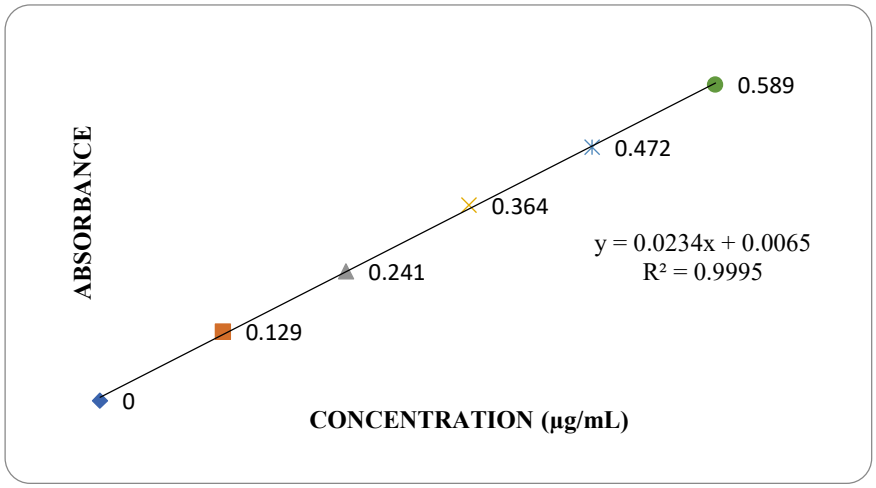

Fig 2: Standard graph of Clindamycin in 0.1N HCL

Standard graph of Clindamycin was plotted as per the procedure in experimental method and its linearity is shown in Table 8.1 and Fig 8.1. The standard graph of Clindamycin showed good linearity with R^2 of 0.999, which indicates that it obeys "Beer- Lamberts" law.

Preformulation parameters of powder blend

Table 7: 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	25.56±0.3	0.57±0.01	0.61±0.01	10.11±0.8	1.13±0.02
F2	24.67±0.3	0.53±0.01	0.68±0.03	10.23±0.5	1.12±0.03
F3	25.56±0.2	0.52±0.06	0.64±0.03	10.34±1.0	1.14±0.06
F4	23.30±0.1	0.50±0.21	0.66±0.12	10.23±0.5	1.12±0.06
F5	22.56±0.1	0.65±0.02	0.59±0.02	11.23±0.8	1.11±0.05
F6	23.89±0.2	0.50±0.04	0.68±0.04	11.34±0.6	1.14±0.03
F7	26.54±0.1	0.59±0.04	0.64±0.05	10.12±0.7	1.13±0.09
F8	23.67±0.3	0.58±0.12	0.58±0.04	10.23±1.0	1.11±0.07
F9	24.34±0.4	0.56±0.02	0.54±0.01	10.23±0.8	1.13±0.02

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 0.50±0.04 to 0.65±0.02 (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 0.54±0.01 to 0.54±0.01 showing the powder has good flow properties. The compressibility index of all the formulations was found to be below 10.34 which shows that the powder has good flow properties. All the formulations has shown the hausners ratio ranging between 1.11 to 1.14 indicating the powder has good flow properties.

Quality Control Parameters For tablets

Tablet quality control tests such as weight variation, hardness, and friability, thickness, Drug content and drug release studies were performed for floating tablets.

***Table 8: In vitro* quality control parameters**

Formulation codes	Weight variation (mg)	Hardness (kg/cm^2)	Friability (%loss)	Thickness (mm)	Drug content (%)	Floating lag time (sec)	Total Floating Time (Hrs)
F1	401.13	4.6	0.34	5.15	99.27	42	8

F2	400.37	4.8	0.46	5.69	98.64	36	9
F3	399.01	5.1	0.29	5.81	100.05	25	10
F4	389.75	4.0	0.62	5.79	99.82	56	8
F5	397.54	5.2	0.72	5.56	97.19	48	9
F6	399.07	4.9	0.69	5.11	98.52	40	9
F7	400.01	5.6	0.28	5.29	99.13	38	8
F8	398.69	4.5	0.47	5.50	97.68	31	8
F9	400.01	4.8	0.52	5.74	98.49	27	8

All the parameters for SR layer such as weight variation, friability, hardness, thickness, drug content were found to be within limits.

***KA In vitro* drug release studies**

Table 9: Dissolution data of Floating tablets

Time (H)	% OF DRUG RELEASE								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
0.5	32.62	28.38	16.23	44.97	21.82	20.31	11.22	13.49	9.07
1	45.81	33.14	24.38	60.65	36.31	32.38	17.38	15.21	13.31
2	52.20	46.63	35.79	78.16	41.23	36.43	22.45	19.07	21.03
3	56.39	52.82	40.88	80.98	56.96	41.86	29.59	26.17	24.12
4	63.85	60.40	47.54	86.29	64.35	59.75	37.83	35.56	31.13
5	70.34	68.09	58.17	92.73	72.02	65.46	43.26	42.58	39.09
6	87.13	75.46	64.62	97.22	80.75	71.13	53.15	51.27	48.17
7	90.91	81.02	73.93		88.13	78.16	61.29	59.68	55.24
8	98.28	88.59	78.87		96.84	85.77	66.76	67.37	64.36
9		92.36	82.26			90.85	73.27	71.77	68.81
10		98.11	87.15			93.49	78.19	77.42	75.63
11			91.02			98.88	84.64	82.12	79.43
12			100.15				95.49	89.28	87.19

From the dissolution data it was evident that the formulations prepared with Eudragit RSPO as polymer were did not retarded the drug release 12 hours. Whereas the formulations prepared with HPMC K 100 did not retarded the drug release up to 12 hours in the all ratios. In higher concentrations the polymer was unable to retard the drug release. Whereas the formulations prepared with Chitosan were retarded the drug release in the concentration of 50 mg (F7 Formulation) showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 95.49 % in 12 hours with good retardation. Hence from the above dissolution data it was concluded that F3 formulation was considered as optimized formulation because good drug release (100.15%) in 12 hours.

Application of release rate kinetics to Dissolution data for optimised formulation

Table 10: Application kinetics for optimised formulation

Cumula Tive (%) Release Q	Time (T)	Root (T)	Log (%) Release	Log (T)	Log (%) Remain	Release Rate (Cumulative % Release / T)	1/Cum% Release	Peppas Log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
16.23	0.5	0.707	1.210	-0.301	1.923	32.460	0.0616	-0.790	83.77	4.642	4.376	0.266
24.38	1	1.000	1.387	0.000	1.879	24.380	0.0410	-0.613	75.62	4.642	4.229	0.413
35.79	2	1.414	1.554	0.301	1.808	17.895	0.0279	-0.446	64.21	4.642	4.004	0.637
40.88	3	1.732	1.612	0.477	1.772	13.627	0.0245	-0.388	59.12	4.642	3.896	0.746

47.54	4	2.000	1.677	0.602	1.720	11.885	0.0210	-0.323	52.46	4.642	3.743	0.898
58.17	5	2.236	1.765	0.699	1.621	11.634	0.0172	-0.235	41.83	4.642	3.471	1.170
64.62	6	2.449	1.810	0.778	1.549	10.770	0.0155	-0.190	35.38	4.642	3.283	1.359
73.93	7	2.646	1.869	0.845	1.416	10.561	0.0135	-0.131	26.07	4.642	2.965	1.676
78.87	8	2.828	1.897	0.903	1.325	9.859	0.0127	-0.103	21.13	4.642	2.765	1.877
82.26	9	3.000	1.915	0.954	1.249	9.140	0.0122	-0.085	17.74	4.642	2.608	2.034
87.15	10	3.162	1.940	1.000	1.109	8.715	0.0115	-0.060	12.85	4.642	2.342	2.299
91.02	11	3.317	1.959	1.041	0.953	8.275	0.0110	-0.041	8.98	4.642	2.079	2.563
100.15	12	3.464	2.001	1.079		8.346	0.0100	0.001	-0.15	4.642	-0.531	5.173

Drug – Excipient compatibility studies
Fourier Transform-Infrared Spectroscopy

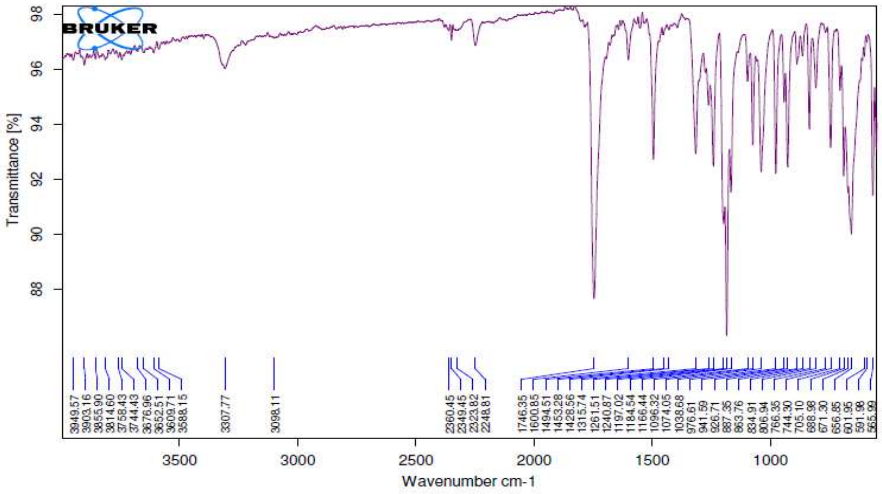

Fig 3: FTIR Spectrum of pure drug

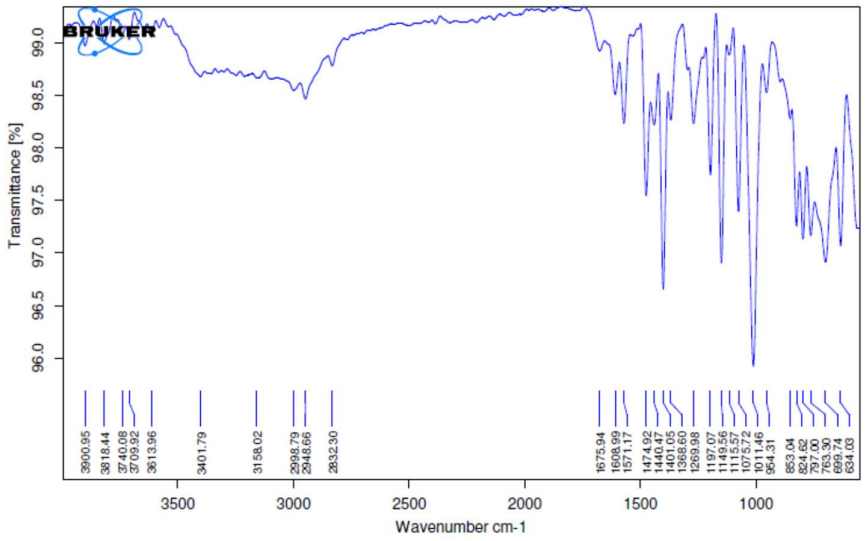

Fig 4: FTIR Spectrum of optimised formulation

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.
Clindamycin 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 study gastro-retentive floating tablets of Clindamycin were successfully prepared by direct compression method using a number of ingredients like Eudragit RSPO, HPMC K 100, Chitosan, Sodium Bicarbonate, Talc and Magnesium stearate. For each formulation blend of the drug and excipients were prepared and evaluated, the tablets were compressed by direct compression method. Compatibility study revealed that there was no interaction between the drug and the excipients in the formulation. Pre-compression parameters were tested for each and every formulation batch and were found to be satisfactory. *In-vitro* drug release studies were carried out for all prepared formulation and from that concluded F3 formulation has shown good results finally concluded release kinetics to optimised formulation (F3) has followed Kors mayer peppas release kinetics mechanism.

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