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[Research article]

Formulation and Evaluation of Gabapentin Mucoadhesive Gastro Retentive Tablets.

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ABSTRACT

The present research work was an attempt to Formulate and Evaluate Gabapentin Gastroretentive mucoadhesive tablets to prolong gastric residence time and increase drug absorption further increasing the bioavailability. The tablets were prepared by direct compression method using mucoadhesive polymers like Carbopol 934P, Sodium Carboxy Methyl Cellulose (SCMC), Sodium alginate along with other standard excipients like Microcrystalline cellulose, Magnesium stearate and Aerosil . FTIR studies confirmed the absence of any drug/polymers/excipients interactions. The prepared tablets were evaluated by different parameters such as Thickness, Weight variation, Hardness, Content Uniformity, Swelling Index and Mucoadhesive strength. Indigenously fabricated assembly was used to measure the Mucoadhesive strength of the Mucoadhesive tablets, and goat gastric mucosa was used as a model tissue. Mucoadhesive strength increased with increasing Polymer concentrations. The tablets were also evaluated for in vitro drug release in 0.1N HCl for 12 h in USP Type II dissolution apparatus. Among all the formulations (F-I to F-XII) prepared, batch F-IV (0.5% C-934P) gave relatively slow release of Gabapentin over 12 h when compared to other formulations The *in-vitro* data is fitted in to different kinetic models and the best-fit was achieved with the Peppas model. The optimized formulation F-IV followed Zero order release kinetics followed by non-fickian transport. Mucoadhesive tests assured the prolonged Gastro retention of tablets. It also showed no significant change in physical appearance, Drug content, Mucoadhesive strength or *in-vitro* dissolution pattern after storage at 45^0 C at 75 % RH for a period of 3 months

Keywords: Gastroretentive, Gabapentin , Mucoadhesive, Swelling Index, Sodium CMC, Sodium alginate.

INTRODUCTION

Historically oral route represents the predominant and most preferable route of drug delivery for the administration of therapeutic agents. For a number of drugs this approach is generally adequate. However, numerous drugs remain poorly available when administered by this route. Among the other reasons this can be due to 1) Low mucosal permeability of drug ii) permeability restricted to a region of GIT, iii) low or very low solubility of compound which results in low dissolution rate in the mucosal fluids and elimination of a fraction of the drug from alimentary canal prior to absorption iv) Lack of stability in the gastrointestinal environment, resulting in a degradation of the compound prior to its absorption[1]

The concept of regulating drug delivery in the human body has been existence for many years because of major benefits such as improved patient compliance and decreased side effects.

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Conventional oral dosage forms often produce fluctuations of drug plasma level that either exceed safe therapeutic level or quickly fall below the minimum effective level; this effect is totally dependent on the particular agent's biologic half life, frequency of administration, and release rate. Many innovative methods have been developed in the last few years for obtaining modified drug release.[2]

Numerous oral controlled release drug delivery systems have been developed to prolong drug release. An important prerequisite for successful performance for an oral controlled release drug delivery system is that the drug should have good absorption throughout the whole gastrointestinal tract (GIT) to ensure continuous absorption of released drug . But for large number of drugs, transport across the intestinal epithelium in each segment of GIT is not uniform and often limited to a particular segment (window) only.[3] So, the oral controlled release drug delivery becomes more difficult due to the inability to restrain and localize the drug delivery system within the desired region of GIT. Under such conditions, one of the most feasible approach for achieving a prolonged and predictable drug delivery profile in GIT is to control the gastric residence time by designing a delivery system that is able to reside in stomach or preferably prior to absorption window that would increase the absorption of drugs[4]

Gabapentin, an analog of GABA, originally developed as an anticonvulsant but now it is used in the treatment of amyotrophic lateral sclerosis (ALS) painful neuropathies, hot flashes (cancer-and/or postmenopausal-related), Fibromyalgia, Neuralgia/neuropathy/chronic pain, prevention of migraine etc with minimal side effect profile when compared to other drugs. However, due to its absorption window in upper part of GIT through a suitable L-amino acid transport system, short half-life (5-7h) and low bioavailability at higher doses due to saturation of amino acid transporters traditional immediate-release Gabapentin solid dosage forms need to be administrated three to four times a day.[5,6]

The aim of this research work was to develop a controlled release Gabapentin oral dosage form which can retain the drug in the stomach for prolonged duration by mucoadhesive nature of the dosage form and show improved bioavailability by virtue of slower release rate that avoid saturation of carrier mediated transport of conventional dosages. Among the several approaches like mucoadhesion, flotation, sedimentation, expansion, modified shape systems etc.[7] Effervescent systems are not suitable for this type of drug because due to continuous effervescence burst release of drug may occur which leads to decreased bioavailability. Mucoadhesion is choosen as best approach for prolonging the gastric residence time, increasing absorption rate and enhanced bioavailability of the drugs due to a high surface to volume ratio, a much more intimate contact with the mucus layer.[8] With the intention of fabricating Gabapentin mucoadhesive single unit dosage form, the work was initiated. In this manuscript we highlighted how the dosage form was designed, evaluated. It was hypothesized that gastro retention of the drug would be enhanced by mucoadhesive nature of the dosage form.

MATERIALS AND METHODS

Materials

Gabapentin was received as a gift sample from Spectrum Pharma Labs , Hyderabad. Sodium Alginate, Carbopol 934P and Sodium CMC were obtained from Triveni Chemicals, Mumbai. Microcrystalline cellulose (PH102), Magnesium stearate and Aerosil were obtained from S.D Fine Chem, Mumbai. All the reagents and chemicals used were of analytical grade.

METHODS

Drug-Excipients compatibility studies

spectral analysis of pure drug and physical mixture of drug and different excipients which are used for preparation of tablets was studied by FTIR. Potassium bromide (KBr) disks were prepared by mixing few mg of sample with potassium bromide by compacting in a hydrostatic press under vacuum at 6-8 tons pressure. The resultant disc was mounted in a suitable holder in IR spectrophotometer and the IR spectrum was recorded from 4000 cm^{-1} to 400 cm^{-1} in a scan time of 12 minutes. The resultant spectrum was compared for any spectral changes. They were observed for the presence of characteristic peaks for the respective functional group in the compound.

Formulation of Gabapentin Mucoadhesive tablets

Gabapentin tablets were prepared by Direct compression Method.[9] In all formulations the drug concentration was kept constant. Different Mucoadhesive polymers like Carbopol 934P ,Sodium CMC and Sodium alginate were used in

different concentrations like 0.25,0.5,0.75. All the formulation contained 1.5% magnesium stearate and 0.5% Aerosol . MCC was used as filler. The compositions of different formulations trials with different polymers are presented in Table 1. Accurately weighed quantities of polymer and Avicel were mixed in geometrical ratio. To this mixture, required quantity of Gabapentin was added and mixed slightly with pestle. This mixture was passed through 60# mesh (0.425 mm diameter), collected in a plastic bag and blended for 5 min. The required quantity of magnesium stearate and talc were added, and the final blend was again passed through 60#. The blend was mixed thoroughly for 5 min and compressed into tablets of average weight of 850 mg with same force using round shaped punches.

Table -1: Composition of Various Formulations

Ingradients	F-I (mg)	F-II (mg)	F-III (mg)	F-IV (mg)	F-V (mg)	F-VI (mg)	FVII (mg)	F-VIII (mg)	FIX (mg)	F-X (mg)	F-XI (mg)	F-XII (mg)
Gabapentin	450	450	450	450	450	450	450	450	450	450	450	450
Carbopol (934p)	112.5	-	-	225	-	-	337.5	-	-	112.5	112.5	-
Sodium Alginate	-	112.5	-	-	225	-	-	337.5	-	-	112.5	112.5
Sodium CMC	-	-	112.5	-	-	225	-	-	337.5	112.5	-	112.5
MCC (PH 102)	270.5	270.5	270.5	158	158	158	45.5	45.5	45.5	158	158	158
Magnesium Stearate	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
Aerosil 200	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5
Total Weight	850	850	850	850	850	850	850	850	850	850	850	850

Evaluation of Mucoadhesive tablets

The prepared tablets were evaluated for Pre and Post compression parameters.

Pre compression parameters [10]

The flow properties of powder blend (before compression) were characterized in terms of angle of repose, tapped density, bulk density, Carr's index and Hausner's ratio .

Angle of repose

A funnel was kept vertically in a stand at a specified height above a paper placed on a horizontal surface. The funnel bottom is closed and 10 gm of powder is filled in funnel. Then funnel was opened to release the powder on the paper to form a smooth conical heap, is found by measuring in different direction. The height of the heap was measured by using scale. The value of angle of repose is calculated by using the following formula:

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

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

Where, h- height of the heap

r- Radius of the heap

Bulk density

- Around 10g (M) of sample was weighed and transferred to a 50ml measuring cylinder.
- The volume (V0) was noted.
- B.D was calculated using the following formula ; B.D = M / V0

Tapped density

- The measuring cylinder of the previous test was mounted on the Tapped density apparatus (USP I)

- Tapped 500 times and volume was noted as Va.
- Tapped 750 times and volume was noted as Vb. (if the difference between Va and Vb was more than 0.2% then tapped for more 1250 times)
- The final volume was noted as Vf.
- T.D was calculated using the following formula –T.D = M / Vf

Hausner's ratio (H.R)

- Hausner's ratio was calculated using the following formula;
  H.R = T.D / B.D

Compressibility index (C.I)

- Compressibility index was calculated using the following formula:
  C.I = 100 X (1 – 1/H.R.)

Post compression parameters

i. Thickness and diameter

Physical dimensions of the tablet such as thickness and diameter is essential for consumer acceptance and tablet uniformity. The thickness and diameter of the tablet was measured using vernier callipers. It is expressed in mm. Five tablets were used and average values were calculated.[11]

ii. Hardness

It indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. The value was noted in kg/cm^2.Three tablets were randomly picked and the hardness of the tablets was determined.[12]

iii. Weight variation

Randomly selected twenty tablets were weighed individually and to geather in a single pan balance. The average weight was noted and standard deviation was calculated . The tablet passes the test if not more than two tablets fall outside the percentage limit and none of the tablet differs by more than double percentage limit.[13]

% Deviation = $(W_{avg} – W_{inital}) / W_{avg} \times 100$

where, W_{avg} - average weight of tablet, W_{inital} – individual weight of tablet.

iv. Friability

Tablet strength was tested by Roche Friabilator. It is expressed in percentage (%). Ten tablets were initially weighed (W0) and into friabilator.[14] The Friabilator was operated at 25rpm for 4min or run up to 100 revolutions. The tablets were weighed again (W). The % friability was then calculated by:

% Friability = $(W_0\text{-}W/ W_0) \times 100$

where, W_0 - initial weight of tablets, W - final weight of tablets.

% Friability of tablets less than 1% are considered acceptable.

v. Drug content

Ten tablets were powdered in a mortar**.** Weighed accurately the quantity equivalent to 100mg of Gabapentin and transferred to a 100mL volumetric flask containing 10mL of 0.1N HCl and shake for some time and make up the volume up to 100mL with 0.1N HCl (i.e. 1000µg/mL) . Pipette out 10mL from the primary stock solution into another 100mL volumetric flask and make up the volume with 0.1N HCl (i.e.100µg/mL). The absorbance was measured by UV-Visible spectrophotometer at 210nm using 0.1N HCl as blank [15]

vi. Invitro drug release study

Release of the prepared tablets was determined up to 12hr using USP XXIV (TypeII) dissolution rate test apparatus (Model TDT 6P Electro lab Mumbai). 900 ml of 0.1N HCl was used as dissolution medium. The rotation of paddle was fixed at 50rpm and the temperature of 37±0.5^oC was maintained throughout the experiment. Samples of 5ml were withdrawn at known time intervals and were placed with same volume of fresh dissolution media after each with drawn. The samples were analyzed spectrophotometrically for drug contents on double beam UV-Visible spectrophotometer at 210 nm.[16,17]

vii. Swelling studies

The swelling studies were carried out by determining the swelling index using USP type I apparatus (basket) and revolved at 100 rpm for 12hr. At intervals of 2 hr, tablets were removed from basket and weighed (Wt). The swelling index was calculated by using the formula given below.

Swelling index = ((Wt-Wo)/Wo)*100 [18]

Wt= weight of swollen tablet at each time interval,

Wo= initial weight of tablet

viii. In - vitro Mucoadhesion study (In-vitro wash-off test)

The mucoadhesive property of the tablet was evaluated by an *in-vitro* adhesion testing method

known as the wash-off method. Freshly excised piece of intestinal mucosa (2×2 cm) from sheep was mounted on to the glass slide (3×1 inch) with cyano acrylate glue. The tablet was sticked to the tissue by applying slight pressure with thumb and the support was tied to the paddle with cotton thread of a USP dissolution apparatus containing 900ml of distilled water and rotated at the speed of 25 rpm. When the dissolution apparatus was operated, the tissue was given a slow, regular rotation in the test fluid (distilled water) at 37^0C contained in the vessel. The test was conducted till the tablet remain sticked to the tissue. The time of adherence is noted known as mucoadhesion time. [18]

ix. *Ex- vivo* Mucoadhesion strength

Mucoadhesion strength of the tablet was measured on the modified physical balance. The apparatus consists of a modified double beam physical balance in which additional weight has been added to right pan, to make the right side weight equal with left side pan. A small beaker was kept in a beaker filled with 0.1 N HCl Buffer pH 1.2, which was then placed under the pan. Fresh goat intestinal mucosa was used as the membrane and 0.1 N HCl Buffer pH 1.2, was used as the moistening fluid. The goat intestinal mucosa was obtained from local slaughter house and kept in a Krebs buffer during transportation. The underlying mucus membrane was separated using surgical blade and washed thoroughly with 0.1 N HCl Buffer pH 1.2, and tied over the smaller beaker using a thread. The smaller beaker was kept in large glass beaker filled with 0.1 N HCl Buffer pH 1.2 up to the upper surface of the goat intestinal mucosa . The one side of the tablet was attached to the right arm/pan of the balance and then the beaker was raised slowly until contact between goat mucosa and mucoadhesive tablet was established. A preload of 5g was placed for 5 min (preload time) to established adhesion bonding between mucoadhesive tablet and goat intestinal mucosa. The preload and preload time were kept constant for all formulations. After the completion of preload time, preload was removed from the glass slide and water was then added in the plastic bottle in left side arm by burette at a constant rate of 100 drops per min. The addition of water was stopped when mucoadhesive tablet was detached from the goat intestinal mucosa. The weight of water required to detach mucoadhesive tablet from intestinal mucosa was noted as mucoadhesion strength in gms. From the mucoadhesion strength the force of adhesion (N) was calculated.[19]

$$\text{Force of adhesion (N)} = \frac{\text{Mucoadhesive Strength (gm)}}{1000} \times 9.81$$

x. Stability studies of Optimized formulation

In order to determine the change in evaluation parameters, in vitro drug release profile and swelling index on storage, stability study of optimized formulation was carried out at accelerated storage condition at temperature 40°C ± 2°C and 75% ± 5% RH in a Stability chamber for 3 months. Sample were withdrawn after 3 months and evaluated for change in physical and chemical variations, in-vitro drug release , swelling index studies and Mucoadhesive studies.[20,21]

RESULTS

FTIR Studies

FTIR spectral analysis was carried out to rule out the possibility of drug-excipient interaction.Vibrational spectroscopy (IR) describes same kind of molecular information and can be used to supplement or complement each other. Middle IR (400–4000cm–1; vibration-rotation region) was used for analytical purpose. The atoms held by a chemical bonds are the main participants in vibration. Vibrations depend on mass of two vibrating atoms, force constant of bond between two atoms and other atoms attached. Thus vibrations are characteristic for a group. In FTIR spectrogram results, the functional region is important for stretching and the fingerprint region for bending.

Fig.1: FTIR spectrum of Gabapentin

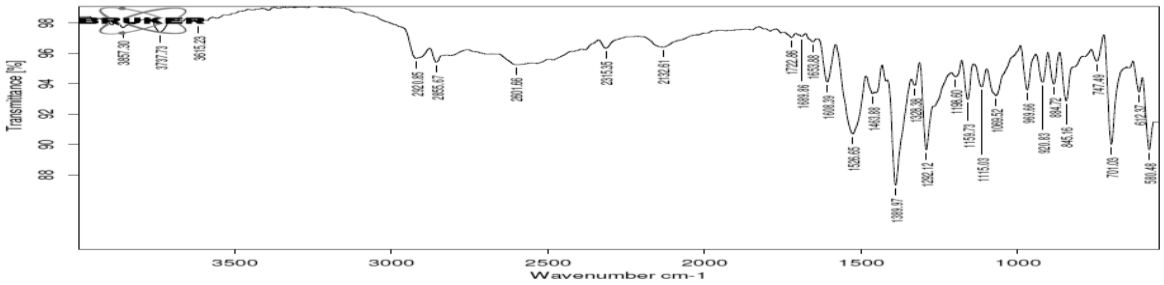
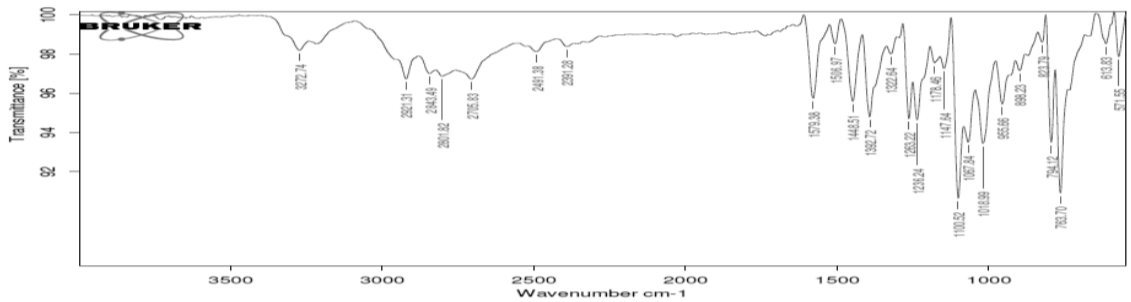


Fig. 2: FTIR spectrum of Best Formulation



Precompression parameters

The various precompression parameters like Angle of repose, Bulk density, Tapped density, Compressibility Index and Hausner ratio for the lubricated blend are determined and given below (Mean ±S.D).

Table No.2: Precompression parameters

Formulation code	Bulk density(gm/ml)	Tapped density (gm/ml)	Hausner ratio	Compressibility Index	Angle of repose
F-I	0.432± 0.02	0.494± 0.04	1.154± 0.02	13.3± 0.10	$27^0 70^1$ ± 0.01
F-II	0.402± 0.03	0.452± 0.03	1.124± 0.04	11.0± 0.09	$26^0\ 12^1$± 0.05
F-III	0.453± 0.04	0.532± 0.03	1.178± 0.04	15.11± 0.05	$29^0 10^1$± 0.05
F-IV	0.420± 0.01	0.495± 0.04	1.162± 0.04	13.9± 0.04	$25^0 51^1$± 0.01
F-V	0.422± 0.02	0.521± 0.03	1.18± 0.02	11.5± 0.07	$24^0 32^1$± 0.04
F-VI	0.438± 0.02	0.486± 0.02	1.14± 0.05	15.3± 0.05	$30^0 19^1$± 0.01
F-VII	0.414± 0.04	0.505± 0.05	1.173± 0.03	14.7± 0.10	$26^0 12^1$± 0.10
F-VIII	0.428± 0.02	0.512± 0.02	1.184± 0.05	15.5± 0.08	$32^0 94^1$± 0.10
F-IX	0.432± 0.02	0.471± 0.05	1.187± 0.04	15.7± 0.01	$31^0 20^1$± 0.10
F-X	0.438± 0.03	0.467± 0.02	1.162± 0.02	13.9± 0.06	$25^0 57^1$± 0.05
F-XI	0.416± 0.03	0.494± 0.02	1.139± 0.01	12.2± 0.09	$29^0 16^1$± 0.01
F-XII	0.407± 0.02	0.452± 0.03	1.150± 0.02	13.0± 0.12	$28^0 94^1$± 0.10

Each value represents as Mean±SD of three determinants

Post compression parameters: The Various Post Thickness, % Friability and % Drug content were compression parameters like Weight variation Hardness, determined and given below

Table No. 3 : Post compression parameters

Formulation code	Weight variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	% Friability	% Drug content
F-I	851 ± 3.3	7.2 ± 0.1	5.42±0.062	0.042± 0.01	99.75± 0.260
F-II	850± 2.8	7.0± 0.4	5.32±0.042	0.051± 0.05	100.2± 0.135
F-III	851± 2.9	7.3± 0.2	5.46±0.060	0.041± 0.00	101.3± 0.40
F-IV	851± 2.4	7.4± 0.1	5.44±0.060	0.044± 0.02	100.2± 0.10
F-V	849± 3.3	7.1± 0.2	5.36±0.040	0.053± 0.04	101.5± 0.90
F-VI	850± 1.9	7.5± 0.1	5.48±0.030	0.043± 0.03	99.30± 0.70
F-VII	849± 3.3	7.5± 0.0	5.45±0.022	0.038± 0.05	98.88± 0.50
F-VIII	850± 1.6	7.0± 0.3	5.36±0.052	0.054± 0.02	99.54± 0.10
F-IX	851± 2.4	7.4± 0..1	5.48±0.012	0.046± 0.05	99.11± 0.60
F-X	851± 1.4	7.1± 0.1	5.47±0.062	0.046± 0.04	100.8±0.20
F-XI	852± 1.9	7.3± 0.2	5.45±0.052	0.044± 0.01	99.11± 0.90
F-XII	849± 1.7	6.9± 0.3	5.42±0.042	0.051± 0.05	100.2± 0.70

Each value represents as Mean±SD of three determinants

In vitro drug release studies

Table No. 4 :Invitro drug release data of Formulations F-I to F-VI

S.NO	Time (Hrs)	F-I(%)	F-II(%)	F-III(%)	F-IV(%)	F-V(%)	F-VI(%)
1	0	0.00± 0.00	0.00± 0.00	0.00± 0.00	0.00± 0.00	0.00± 0.00	0.00 ± 0.00
2	1	43.03± 0.19	51.4± 0.98	72.6± 1.99	14.27± 1.66	21.3± 1.43	56.49± 1.04
3	2	51.6± 0.23	67.8± 0.43	94.5±0.49	24.53±0.84	27.1±0.29	64.9±0.39
4	3	58.5± 0.61	84.6 ± 0.41	101.1±0.28	27.9± 0.79	34.9±0.33	76.8±0.44
5	4	64.5± 0.40	92.4 ± 0.29		32.1± 0.68	42.9± 0.78	84.40±0.28
6	5	68.7± 0.55	98.6 ±0.63		37.8± 0.65	54.4 ±0.60	91.9±0.21
7	6	78.4± 0.39			41.2± 2.61	60.4±0.42	99.24±0.75
8	7	85.2± 0.28			48.03±0.98	70.8 ±0.41	
9	8	92.5± 0.36			56.3± 0.68	82.4 ±0.98	
10	9	99.79± 0.33			68.5± 0.40	90.2 ±0.20	
11	10				79.9± 1.09	98.6 ±0.61	
12	11				91.3± 0.63		
13	12				99.95± 0.18		

Fig. 3: Invitro drug release profile of formulations F-I to F-VI

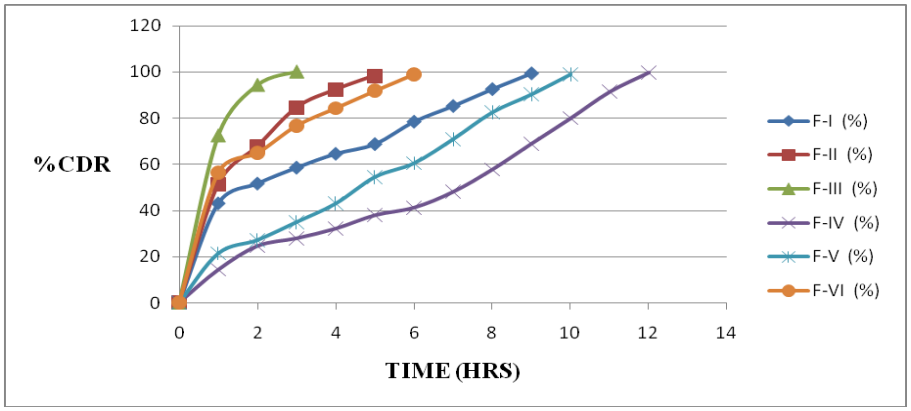
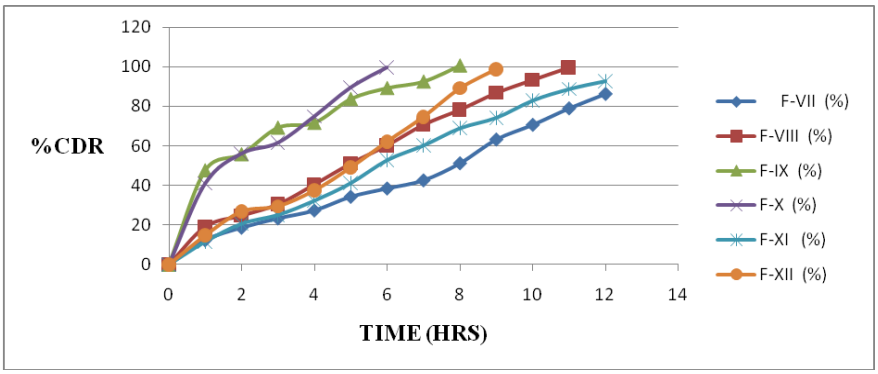


Table No. 5 :Invitro drug release data of Formulations F-VII to F-XII

S.NO	Time (Hrs)	F-VII(%)	F-VIII(%)	F-IX(%)	F-X(%)	F-XI (%)	F-XII(%)
1	0	0.00± 0.00	0.00± 0.00	0.00± 0.00	0.00± 0.00	0.00± 0.00	0.00± 0.00
2	1	12.4±2.01	19.2± 1.66	47.8± 1.21	41.02± 3.67	11.6± 1.60	14.8± 3.30
3	2	18.7± 0.53	24.8± 0.49	55.9± 0.74	56.12±1.44	20.7± 1.30	26.91± 1.23
4	3	23.4± 0.41	30.6± 0.32	69.4± 1.44	61.54± 0.63	25.13± 1.29	29.56± 0.41
5	4	27.4± 0.42	40.6± 1.23	71.8± 0.48	74.8± 2.04	32.3± 1.43	37.6± 1.50
6	5	34.3± 0.36	51.2± 0.57	83.9 ± 0.55	89.4± 3.00	41.2 ± 0.71	49.2 ± 2.36
7	6	38.5± 0.53	60.4± 1.12	89.4 ± 0.21	99.55 ±0.56	52.8± 0.56	62.3±0.31
8	7	42.6±0.85	70.8± 3.00	92.7 ± 0.45		60.2 ± 0.86	74.8± 1.90
9	8	51.2± 0.73	78.4 ± 1.67	100.1± 0.73		68.9± 0.41	89.2 ± 1.19
10	9	63.2± 1.07	86.9 ± 0.63			74.2± 0.73	99.16± 0.33
11	10	70.6± 0.36	93.45 ± 1.92			82.9± 0.68	
12	11	78.9± 0.96	99.72 ± 0.46			88.7± 1.08	
13	12	85.3 ± 1.96				92.7± 0.80	

Fig. 4: Invitro drug release profile of formulations F-VII to F-XII



Swelling Studies

The results of swelling index of Gabapentin tablets in 0.1 N HCl were tabulated below

Table No. 6: Swelling index of Gabapentin Tablets in 0.1 N HCl

S.No	Time(Hrs)	F-I	F-II	F-III	F-IV	F-V	F-VI
1	1	89.3±0.30	43.3±0.20	56.4±0.25	102.4±0.15	50±0.20	62.2±0.15
2	2	94.03±0.15	56.6±0.15	65.5±0.10	116.2±0.30	63.2±0.3	66.6±0.30
3	4	112.1±0.10	66.6±0.10	71.1±0.17	121.4±0.20	71.1±0.15	87.7±0.05
4	6	115.1±0.3	75.5±0.20	80.2±0.15	128.7±0.10	78.8±0.10	93.3±0.10
5	8	117.1±0.15	80.1±0.17	86.8±0.37	129.2±0.15	85.5±0.25	97.5±0.10
6	10	116.4±0.25	79.8±0.15	83.3±0.20	128.3±0.05	83.9±0.05	96.2±0.25
7	12	115.8±0.10	78.9±0.3	82.7±0.47	127.9±0.10	83.1±0.15	95.8±0.3

Table No. 7: Swelling index of Gabapentin Tablets in 0.1 N HCl

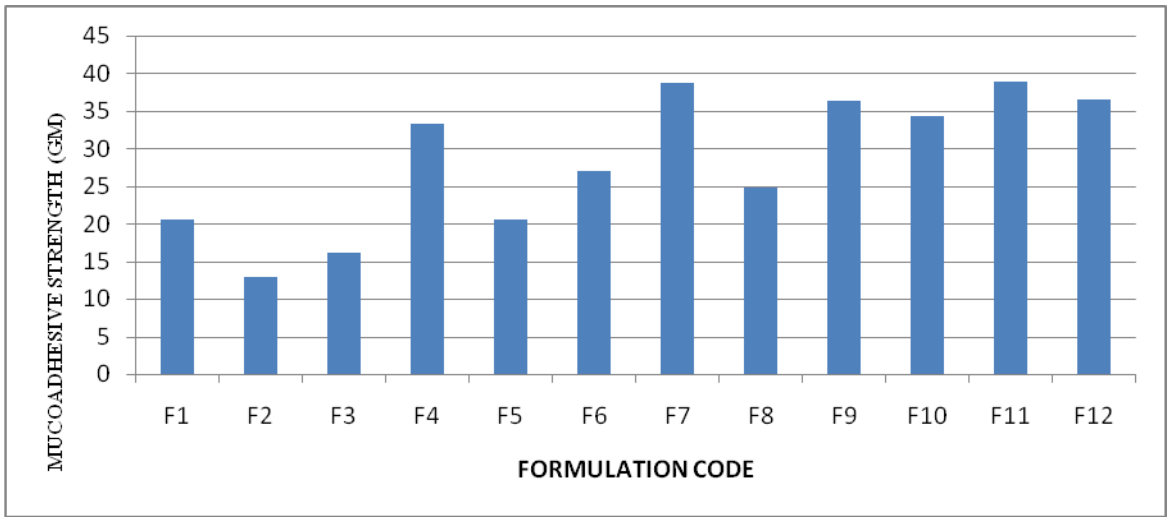
S.No	Time(Hrs)	F-VII	F-VIII	F-IX	F-X	F-XI	F-XII
1	1	108±0.10	76.6±0.20	71.1±0.17	78.8±0.17	109±0.10	76±0.25
2	2	117.5±0.20	83.3±0.15	80±0.15	89.2±0.10	115±0.37	85.8±0.30
3	4	124.5±0.15	91.1±0.20	97±0.10	100.2±0.20	122±0.30	97.5±0.10
4	6	129.2±0.25	97.7±0.25	108.8±0.20	104.2±0.25	135±0.10	100.2±0.17
5	8	134.9±0.05	102.1±0.30	109.1±0.25	106.6±0.17	140.2±0.05	101.9±0.05
6	10	133.1±0.10	101.7±0.15	106.2±0.20	105.9±0.05	139.8±0.25	101.6±0.10
7	12	132.7±0.10	101.2±0.17	105.8±0.30	104.7±0.10	138.9±0.10	101±0.25

Mucoadhesive studies

Table No. 8: Mucoadhesive Strength(gm) and detachment time of all Formulations

Formulation code	Mucoadhesive Strength(gm)	Mucoadhesion Force (N)	Detachment time(min)
F- I	19.59±2.53	0.192	360
F-II	13.98±1.23	0.137	260
F-III	17.06±1.65	0.167	352
F-IV	30.83±2.70	0.302	600
F-V	20.50±2.27	0.201	410
F-VI	26.92±3.00	0.264	552
F-VII	38.68±2.40	0.379	600
F-VIII	24.79±1.60	0.243	520
F-IX	33.29±3.31	0.326	570
F-X	34.37±2.15	0.337	565
F-XI	38.97±3.10	0.382	600
F-XII	36.56±2.22	0.358	540

Fig. 5: Mucoadhesive Strength of various formulations



Stability studies of optimized formulation:

Table No. 9: Stability data of optimized formulation Physico-chemical parameters

Parameter	Initial	After 3 months at 40°C/75%RH
Weight Variation	851± 2.4	851± 2.1
Thickness(mm)	5.43±0.062	5.42±0.052
%Friability	0.044 ± 0.02	0.046± 0.01
Hardness(kg/cm^2)	7.4± 0.10	7.5± 0.10
% Drug content	100.2± 0.10	99.77± 0.15
Mucoadhesive Strength(gm)	30.83± 2.70	29.64 ± 2.58

DISCUSSION

Drug Excipient Compatibility Studies

The pure drug Gabapentin and the solid admixture of drug and various polymers used in the preparation of Mucoadhesive tablets were characterized by FTIR spectroscopy to know the compatibility. As shown in the figure 1-2, there was no significant difference or the characteristic peak of pure drug was unchanged in spectrum of optimized formulation (F-IV).

Precompression parameters of tablets

In the present study, direct compression was adopted for tabletting. Pure drug showed good flow properties. The formulations F-I to F-XII have, Bulk density varied between 0.397 gm/ml to 0.45 gm/ml, Tapped density was 0.452 gm/ml to 0.532 gm/ml, the compressibility index was 11.0 to 15.7, Hausner ratio was 1.124 to 1.187and angle of repose was $26^0 10^1$ to $32^0 94^1$. It indicates the developed formulation possesses good flow properties.Hence powder mixture was found suitable for direct compression method.

Post compression parameters of tablets

Post compression parameters are given in the table 3. The formulations F-I to F-XII have, Average weight vary between 849 mg to 852 mg, Hardness was vary between 6.9 to 7.5 kg/cm^2, Thickness was vary between 5.32 to 5.48 mm, percentage of Friability was vary between 0.038 % to 0.054%, percentage of Drug content was varied between 98.88 % to 101.5 %. It indicates all the above results were in limits.

In vitro drug release studies

Formulations containing 0.25 and 0.5%w/w of Carbopol 934P (F-I and F-IV) exhibited release over 09 and 12 hrs respectively. On further increasing polymer concentration i.e. at 0.75% polymer concentration(F-VII) only 85.3% of drug was released .This clearly indicates that release rate was influenced by polymer concentration. Among the formulations containing Sodium alginate polymer (F-II, F-V, F-VIII) only F-VIII (containing 0.75% polymer concentration) retarded the drug release for a period of 11 hrs. The trials made with Sodium CMC are not successful because of faster hydration rate of polymer. Various polymer combinations are also tried at 0.5% concentration in equal ratios(1:1). Among them formulation F-XI containing C-934P and Sodium alginate (0.25% and 0.25%) at 0.5% concentration released only 92.7% of drug at the end of 12 hrs. This can be due to higher viscosity of Carbopol polymers and due to cross linking of sodium alginate polymers. Among all the formulations the formulation F-IV containing 0.5% Carbopol showed 99.95% of drug release at the end of 12 hrs. So it is the best formulation releasing the drug at a controlled rate for a period of 12hrs increase drug absorption further increasing the bioavailability.

Release Kinetics

To analyze the mechanism of drug release from the matrix tablets, the release data was fitted into various mathematical models viz., Zero order, first order and Highuchi equation .[22,23] The dissolution data was also fitted to the well known experimental equation (Koresmeyer's Peppas equation), which is often used to describe the drug release behavior from polymer systems .

$$Mt / M\infty = Kt^n$$

Where, Mt is the amount of drug release at time t, $M\infty$ is the amount of drug release after infinite time; K is a release rate constant incorporating structural and geometrical characteristics of the tablet and n is the differential exponent indicative of the mechanism of drug release.

To clarify the release exponent for the different batches of matrix tablets, the log value of % drug release was plotted against log time. A value of n=0.45 indicates Fickian (case I) release; >0.45 but <0.85 for non Fickian (anomalous) release; > 0.89 indicates super case II type of release. Case II gradually refers to the erosion of the polymeric chain and anomalous transport (non- Fickian) refers to a combination of both diffusion and erosion controlled drug release.[24]

Mechanism of drug release [25,26]

As observed from the various plots , all the formulations followed Zero order kinetics and best explained by korsmeyer peppas model which have greater regression values than the Higuchi model. The optimized formulation F-IV followed zero order kinetics and best explained by korsmeyer peppas model. Based on the n value it followed non-fickian transport mechanism.

Swelling studies

The Swelling Index of tablets as shown in the table 6,7 were directly proportional to the concentration of the polymer, as the polymer concentration increases there was increase in the Swelling Index. On comparing the Swelling Index, it was observed that F-XI containing (0.25% Carbopol + 0.25% Sodium alginate) showed maximum Swelling Index.

In–vitro mucoadhesive study

The *in-vitro* mucoadhesive study was performed on modified physical balance and measures the mucoadhesive strength(g) requires to detach the tablet. The Mucoadhesive strength ranged between 13.98 to 38.97 g. As the concentration of polymers increases Mucoadhesive strength and residence time increases. Detachment time ranged between 260 to more than 600 mins. Although the maximum value of Mucoadhesive strength is attained by the combination of polymers, good mucoadhesive strengths are also shown by individual polymers. The Optimized formulation F-IV (0.5% Carbopol 934P) shows good mucoadhesive strength with mucoadhesive time over more than 10 hrs. The results were shown in the table 8.

Stability studies

The stability studies were carried out for the formulations F-IV at 40 ± 2°C/75 ± 5% RH for 3 months. Table 9, shows the values of pre and post compression parameters after stability studies at 40 ± 2°C/75 ± 5% RH for 3 months. The results indicated that the tablets did not show any prominent changes during the study period. This indicates that tablets are fairly stable at storage conditions.

CONCLUSION

The present research was carried out to develop Gastro retentive mucoadhesive tablets of Gabapentin by using various polymers like Carbopol 934P, Sodium CMC and Sodium Alginate alone and in combinations. Formulations containing Carbopol 934p have controlled release for 12 hrs when compared to other polymers. Finally it was concluded from above results, formulation F-IV (0.5% Carbopol) has 99.95% drug release and maintain constant swelling index 102.4% - 127.5% up to 12hr period of time, and good mucoadhesive strength (30.83gm) was selected as optimized formulation . The drug release followed Zero order (R^2 =0.971) and release kinetics best fitted into Korsmeyer-peppas model (R^2 =0.947). It followed Non-Fickian transport mechanism. The study demonstrated that by developing gastro retentive mucoadhesive tablets we can prolong gastric residence time, increasing drug absorption and further increasing the bioavailability. Thus this study can be a promising approach for the delivery of Gabapentin.

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REFERENCES

[1] N.K. Jain. Controlled and Novel Drug Delivery. Edn 1, CBS Publishers and Distributors, 1998.
[2] Banker G.S. Pharmaceutical applications of controlled release: an overview of the past, present, and future. In Medical Applications of Controlled Release, Vol 2, 1984, 1-34.
[3] Brahmankar DM, Jaiswal SB. A Textbook of Biopharmaceutics and Pharmacokinetics A Treatise. Edn 1, New Delhi: Vallabh Prakashan publishers,1995. 64-70.
[4] Kaushik Avinash**,** Dwivedi Abha, Kothari Praveen, Govil Abhinav. Floating Drug Delivery System a Significant Tool for Stomach Specific Release of Cardiovascular Drugs. Int. J. Drug Dev & Res. 4(4), 2012, 116-129.
[5] Drug Bank. Available from URL:http://drugbank.ca/drugs/DB00996(APRD0005)
[6] Tripathi KD. Essential of Medical Pharmacology, Edn 6. New Delhi. Jaypee Brothers Medical Publishers (P) Ltd. 2008, 488.
[7] K Vinod, Vasa Santhosh, S Anbuazaghan, Banji David, A Padmasri, S Sandhya. Approaches for gastrotentive drug delivery systems. International Journal of Applied Biology and Pharmaceutical Technology. 1(2), 2010, 589-601.
[8] Ravi P Soni, Ashish V Patel, Rahul B Patel, Dr. Patel M.R, Dr. Patel K.R,Dr.Patel N.M. Gastroretentive drug delivery systems: a Review. IJPWR. 2(1), 2011, 1-24.
[9] Deshmukh N, Thenge R, Mahajan N. Formulation and evaluation of Bisoprolol fumarate fast dissolving tablet by direct compression techniques. IJPRBS.1(5), 2012, 364-378.
[10] Vinod Kombath, Ravindran *V K* et al. Comparative Study Of Mucoadhesive Polymers Carbopol 974p And Sodium Carboxymethyl Cellulose For Single Unit Dosage of Imatinib Mesylate. Malaysian Journal of Pharmaceutical Sciences.Vol.10(1), 2012, 61–77.
[11] Inderbir singh Gurpreet Arora, Karan Malik, Inderbir Singh, Sandeep Arora and Vikas Rana. Formulation and evaluation of controlled release matrix mucoadhesive tablets of Domperidone using Salvia plebeian gum. Journal of advanced Pharmaceutical Technology and Research, 2(3), 2012, 163–169.
[12] Goswami Dhruba Sankar et al. Formulation And Evaluation Of Mucoadhesive Tablets of Famotidine. Journal Of Pharmaceutical And Biomedical Sciences. 12(06), 2011.
[13] Shaikh A, Pawar YD and Kumbhar ST. Effect of Chitosan and Sodium Alginate on Mucoadhesion and Drug Release of Itraconazole Tablets. International Journal of Research in Pharmaceutical and Biomedical Sciences. 3(1), 2012, 293-297.
[14] Government of India Ministry of Health and Family Welfare. The Pharmacopoeia of India. Delhi, India. Controller of publication, 1997. 1020-1022.
[15] Leon Lachmann, Lieberman HA and Kanig JL. The Theory and practice of Industrial Pharmacy. Special Indian edition, CBS publishers and distributors, 2009. 297-301.

[16] CH.Swarna Kamala Chinthala, K.Srinivas Reddy Kota, M.Hadassah, E.Hepsibha Metilda, S.Sridevi. Formulation and evaluation of gastroretentive floating tablets of Gabapentin using effervescent technology. Int J Pharm Biomed Res. 3(4), 2012, 202-208.
[17] R. Singh Gujral, S Manirul Haque And P Shanker. A Sensitive UV Spectrophotometric Method for the determination of Gabapentin. E-Journal of Chemistry. 6(S1) 2009,S163-S170.
[18] Bhaskar Umarji et al. Formulation And *In-Vitro* Evaluation Of Mucoadhesive buccal Tablets of Furosemide. World Journal Of Pharmacy And Pharmaceutical Sciences. 1(3), 2012;1041-1063.
[19] Sunena Jha, Arun Nanda. Formulation and Evaluation of Sustained Release Mucoadhesive Atenolol Tablets for Gastric Retention . Asian Journal of Biomedical and Pharmaceutical Sciences. 3(19), 2013, 44-49.
[20] Cartensen JT. Drug stability : Principle and Practices. Edn 2. New York : Marcel Dakker; 1995. 538-580.
[21] ICH guideline Q1A- Q1F. Available from URL: www.ich.org/cache/compo/363-272-1.html.
[22] Mockel JE, Lippold BC. Zero order release from hydro-colloid matrices. Pharm Res. 1993; 10:1066-1070.
[23] Highuchi T. Mechanism of sustained action medication: Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J Pharm Sci. 1963; 52:1145-1149.
[24] Peppas NA. Analysis of Fickian and Non-Fickian drug release from polymers. Pharma Acta Helv. 60, 1985, 110-11.
[25] Robinson JR. Sustained and Controlled release Drug Delivery System. Edn 3, Published by: Marcel Dekker, 138-171.
[26] Korsmeyer RW, Gurny R, Docler E, Buri P Peppas NA. Mechanism of solute release from porous hydrophilic polymers. Int J Pharm. 15, 1983, 25-35.

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