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Formulation And Evaluation Of Gastroretentive Mucoadhesive Tablet Of Combination Of Two Drug

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Abstract: For drug delivery due to the simplicity of administration, patient comfort and pliability in the preparation oral drug delivery administration has been the uppermost route. Gastroretentive mucoadhesive tablet of combination of two drugs like Valsartan and Hydrochlorothiazide were prepared by using direct compression technique. Mucoadhesion is a complicated occurrence that includes wetting, adsorption and interpenetration of polymer chains. The formulated tablet of several preparation was characterized during a entire mucoadhesion time, resiliency delay time and percent drug liberation. The several batches were formulated by using a direct compression method utilizing the diversity of mucoadhesive polymers like Carbopol 971, Eudragit RS 100 and exposed to several evaluation variables like in-vitro drug release outline, tablet post compression parameters and physical possessions. The formulated tablet granules are assessed before compression during various parameters such as bulk density, tapped density, angle of repose, compressibility etc. to check the flow possessions of granules. In assessment of Post Compression variables of Gastroretentive high density tablets also various parameters are studied like Weight variation(mg), Friability (%), Hardness(kg/cm^2), Thickness(mm), Drug Content of Valsartan (%), Drug Content of Hydrochlorothiazide (%) etc. The Gastroretentive Mucoadhesive tablet formulation shows best drug release pattern so it is considered as best formulation for the Gastroretentive sustained release drug delivery system. For the sustained release gastroretentive drug delivery system from the evaluation of all types of tablets it is concluded that the Mucoadhesive approach is the best. The stability study of optimized batch of mucoadhesive tablets shows that the formulation is stable.

Keywords: Mucoadhesion, gastroretentive, Valsartan, Hydrochlorothiazide etc.

Introduction

For various hours gastroretentive systems may persist in the gastric area and therefore it may remarkably extend an abdominal residence time of drugs. The bioavailability enhances when extend gastric retention, decreases drug destruction and enhanced solubility during the drugs that are slighter soluble in the elevated pH domain of small intestine [1]. The specific perspective for gastro retention is a mucoadhesive drug delivery. Although the organization is mucoadhesion to an abdominal constituent, drug liberated steadily at a pre-established assess [2,3].

Gastroretentive mucoadhesive delivery systems enhance the residence time of the dosage form in the gastrointestinal tract and contribute constant exposure throughout a dosage form and absorbing tissue that may affects in elevated drug concentration in a district region and therefore elevated drug flux between the absorbing tissue [4]. This could affect in enhanced bioavailability as it is broadly appreciated that the expanse of gastrointestinal drug absorption is associated to the proximity time among the small intestinal mucus.

The binding of a synthetic or natural polymer to a receptor means the mucoadhesion. It is a realistic approach used for drug localization in controlled drug delivery system. In mucoadhesion process, drug is placed in a stomach for a comprehensive time. Mucoadhesion helps for targeting of drugs at particular site along with better control in systemic drug delivery. Drugs that are absorbed along the bounding of mucosal membrane may probe promptly towards blood stream. Gastroretentive formulations does not breakdown by enzymes present in the gastrointestinal tract [5-7].
For a prolong interval of time by interfacial forces mucoadhesion is the condition in which two substances at least one is in organic essence are detain with each other. It is also elucidated that for a prolong interval of time the potential of a substances namely synthetic or biological to stick to a biological tissue [8].

The combination of two drugs is used in this study like Valsartan and Hydrochlorothiazide for the preparation of gastroretentive mucoadhesive tablet. Valsartan is an anti-hypertensive drug that is an angiotensin -receptor blocker (ARB). It is carefully impeding the binding of angiotensin II to angiotensin one that successfully hinder the angiotensin one moderate vasoconstrictive and aldosterone - producing results of angiotensin II and effects in a decline in vascular resistance and blood pressure. Valsartan water solubility is very less, bioavailability is also very less i.e., 20-25 %, and small half-life almost 6 hours. Its definite supercilious absorption in stomach. Therefore, Valsartan has less bioavailability and small half-life, evolve an incessant release organisation may assert the plasma drug concentration in therapeutic window and enhance the therapeutic potency of drug [9,10]. Hydrochlorothiazide is a diuretic of the benzothiadiazide group and it was an acceptable alternate medicine in the administration of gentle to modest hypertension [11].

The major intention of this study was to prepared Valsartan and Hydrochlorothiazide combination drug of mucoadhesive tablets by using Carbopol 971 as a primary polymer and Eudragit RS 100 as a secondary polymer among additional tablet excipients and lubricants to provide superior compressibility by direct compression technique that may give persistent effectual drug release during 8 hours.

Material and Methods

Material

Valsartan and Hydrochlorothiazide was acquired from the Medley Pharmaceuticals Ltd. Research Centre Mumbai. Carbopol 971 acquired from Astron Chemicals, Ahmedabad, Eudragit RS 100 were obtained from Glenmark pharmaceutical Ltd Nashik, Di-calcium phosphate (DCP) from Ajanta pharmaceutical Ltd Aurangabad and Magnesium stearate is also obtained from Astron Chemicals, Ahmedabad.

Method

Pre-formulation studies

Outline of model drugs

a) Loss on drying

Upto a persistent weight was acquired Valsartan and Hydrochlorothiazide sample (1 gm) was transferred towards petri dish and eventually dried in oven at 80°C and 105°C sequentially. The moisture content was later resolute as proportion of weight of moisture indigence to the weight of sample exhibit as a percentage and deliberate by the succeeding formula:

$$\% \text{ Loss on drying} = \frac{\text{Initial weight} - \text{final weight}}{\text{Initial weight}} \times 100$$

b) Solubility

The solubility of Valsartan and Hydrochlorothiazide was resolute using solvents viz. distilled water and methanol.

c) Identification of UV, FTIR, DSC.

UV Analysis

The UV spectrophotometric study was implemented to rectify the λ_{max} of valsartan and hydrochlorothiazide in 0.01M NaOH and 0.1M HCl sequentially and the value is differentiated among standard given in pharmacopeia.

FTIR Investigation

FTIR spectra of Valsartan and Hydrochlorothiazide were enumerate among FTIR spectrophotometer (Shimadzu, Japan). The specific spectrum was differentiated among the spectrum of standard drug in literature. Agreeable studies were accomplished to intimation the probable interactivity throughout Drugs and ingredients used in the preparation. By KBr pellet process drug-excipient interactivity studies were accomplished utilizing FTIR spectrophotometer (Shimadzu). IR compass of clarified drug and optimized preparation were discerned intermediate 4000-400 cm-1.

DSC Analysis

DSC thermograms of the drug Valsartan and hydrochlorothiazide were acquired from DSC (DSC 4000, Perkin-Elmer, New York, NY). The instrument was measured between an indium quality. The specimen (2-4 mg) was enormous (20-300°C) with regard to a continual scanning speed (10°C/min) in clammed aluminium pans, utilize nitrogen expel gas and differentiate among the Standard thermograms in composition.

Formulation and evaluation of Gastroretentive Mucoadhesive tablet

The gastroretentive Mucoadhesive tablet of Valsartan and Hydrochlorothiazide is formulated by direct compression technique. All required excipients are passed across sieve no. 40 and blend in polythene bag during 15min. Then magnesium stearate and talc passed across sieve no 40 is attach to the mixture and again it is mixed for 15 min. then the precompression evaluation parameters of powder blend is carried out and the tablets are compact on a single punch tablet machine. The tablets were circular and flat in shape.

Table 1: Composition of gastroretentive Mucoadhesive tablet

Sr.no	Ingredients	F1	F2
1	Valsartan	80	80
2	Hydrochlorothiazide	12.5	12.5
3	Carbopol 971	150	160
4	Eudragit RS 100	150	140
6	Di-calcium phosphate(DCP)	40	40
7	Magnesium stearate	10	1.5

Formulation and evaluation of powder blend

A. Bulk density

Weighed substance was passed away across a sieve No. 25 to crack up agglomerates and instigate towards a dry 100 mL cylinder, except compressing, the powder was attentively flattened except compressing and the purposeless apparent volume, V_0, was read. In g/mL the bulk density was calculated, using the formula.

$(M)/(V_0)$

Where M = Entire weight of the powder mix and V_0 is the bulk volume of the powder blend.

B. Tapped density

Behind performing the process as specified in the quantification of bulk density the cylinder accommodating the sample was tapped using a mechanically tapped density tester (Electrolab) at a nominal rate of 300 drops/minute that give a secure drop of 14±2 mm. The cylinder was tapped 500 times originally followed by a further tap of 750 times upto variation across following assessment was <2% and later tapped volume V_f, was assessed to the closest graduated unit. Using the formula in g/mL the tapped density was calculated:

$(M)/(V_f)$

Where M = Entire weight of the powder blend and V_f is the tapped volume of the powder blend.

C. Measures of powder compressibility

The compressibility index and Hausner ratio are estimate of the inclination of powder to be compact. Accordingly, they are assessing of the comparatively significance of inter-specific interactivity. Consequently, they are quantity of the comparative significance of inter-specific interactivity. This interactivity is basically fewer important and the bulk and tapped densities will be near in value in a free-flowing powder. During imperfect flowing substance there are rapidly higher interparticle interactivity and a higher variation across the bulk and tapped densities will be noticed. These variations are considered in the compressibility index and the Hausner ratio, that are deliberate using the following formulae [8-11].

Compressibility indication = $(Vr-V_0) *100/Vr$

Where Vr = tapped density; V_0 = Bulk density.

D. Hausner's ratio

The ratio of tapped density to bulk density is a hausner's ratio.

Vr/V_0

V_0 = Bulk density; Vr = Tapped density.

E. Angle of repose

To estimate the repose angle the specified funnel technique was employed. A funnel was fix among its tip at a specified height, 'h' over a graph paper that was allocate on a flat horizontal exterior. The blend was attentively examined across the funnel upto the peak of the conical pile just demented the tip of the funnel. The radius, r, of the root of the conical pile was estimated. Using the following formula, the angle of repose, ɵ, was calculated.

$$\tan(ɵ) = h / r$$

Evaluation of post compression variables of tablets

a) Thickness and diameter

By using digital Vernier Calliper the thickness and diameter of the tablet is estimated.

b) Hardness

Hardness was calculate using Monsanto hardness tester that estimate the pressure essential to crack the diametrical situate tablets by the pressure among coiled spring.

c) Friability

20 tablets were weighed accurately and put down in the Roche friabilator where the tablets were revealed to rotate and persistent shocks emerging from free falls throughout the equipment, behind 100 revolutions, the weighed once more. The friability was resolute as the percentage deprivation in the weight of the tablets. A deprivation of less than 0.5 to 1% in weight is usually examine allowable.

d) Weight variation

Weigh 20 tablets choose at accidental and calculate the average weight. Not more than two of the particular weights diverge from the average by additionally the percentage manifest in table beneath and none diverge by more than two times that percentage.

e) Drug content

It is the quantity adjacent in each and every preparation of tablets. Tablets from formulation was confiscate in a beaker and drip in 100ml 0.1N HCl. Once the drug is liberated entirely the equal sample was withdrawn (around 1ml) and diluted to 10ml with 0.1N HCL and absorbance was taken using UV spectrometer at 229 nm and 271 nm after 24 hrs. % drug was calculated from the standard.

f) In vitro dissolution of tablets

Valsartan and Hydrochlorothiazide Mucoadhesive tablets were retain in dissolution medium 0.1N HCl (900ml) and employ at temperature 37 ± 0.5^0C and rotated at 50 rpm. Newly prepared dissolution medium is used. Paddle type apparatus is used. For every 15, 30, 60, 90, 120, 150, 180, 210, 240,270,300, 330,360,390,420,450 and 480 mins around 3ml of the dissolution medium was pipetted out and the volume was adjusted using by displace among 5ml of 0.1N HCl. The samples

collected were diluted until 10ml examine at 229nm and 271nm using UV spectrometer. And the % drug release was deliberated.

g) Ex-Vivo Mucoadhesion Measurement

Adhesion time of preparation were resolute by using USP type VI (rotating cylinder technique) apparatus, using 0.1N HCl as a medium DISSO 2000 LABINDIA at 37 ± 0.50 C at 100 rpm. By using cyanoacrylate glue the goat gastric mucosa was stick to the cylinder. For 1 minute the tablet was pressed on the mucosa lightly among the finger. Time until that tablet remnants stick to goat gastric mucosa was estimated.

RESULTS AND DISCUSSION

Results for Preformulation parameters of API

a) Loss on drying

As per standard procedure mentioned USP monograph of Hydrochlorothiazide and Valsartan it is expressed as % (LOD) the results are complying with USP standards the loss on drying is calculated.

i) LOD of Hydrochlorothiazide = 0.143%

ii) LOD of Valsartan = 3.6%

b) Solubility studies

Solubility in Distilled water, 0.1N HCl and methanol.

Table 2: Solubility of Valsartan

Solvent	Solubility of Valsartan in (mg/mL)				
	1	**2**	**3**	**Mean**	**SD**
Distilled water	0.175	0.178	0.176	0.176	0.001
0.1N HCl	0.09	0.08	0.08	0.07	0.01
Methanol	2.2	2.6	2.5	2.3	0.21

Table 3: Solubility of Hydrochlorothiazide

Solvent	Solubility of Hydrochlorothiazide in (mg/mL)				
	1	**2**	**3**	**Average**	**SD**
Distilled water	0.292	0.316	0.313	0.297	0.011
0.1N HCl	0.23	0.25	0.29	0.256	0.012
Methanol	0.95	0.92	0.98	0.95	0.02

c) Identification Test

i) Valsartan UV spectroscopy, FTIR and DSC.

UV spectroscopy

By observing the maximum absorption wavelength i.e., λ_{max} identification test was carried out. The λ_{max} was found at about 248 nm and it is as per IP standards.

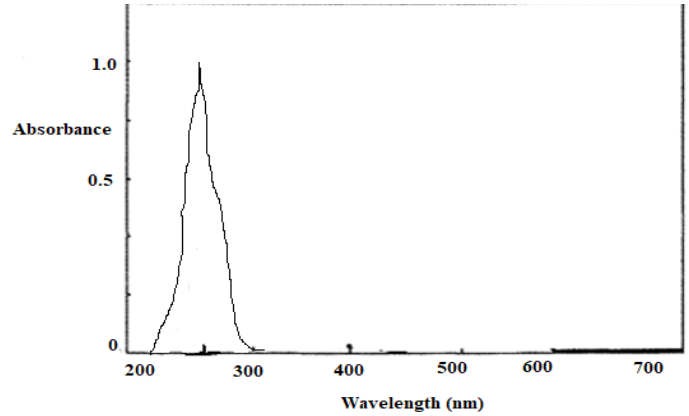

Fig. 1 UV spectra of Valsartan

FTIR analysis

FTIR analysis of illustrative of Valsartan API is carried out and it is found that the spectra are similar to the spectra given in standard literatures.

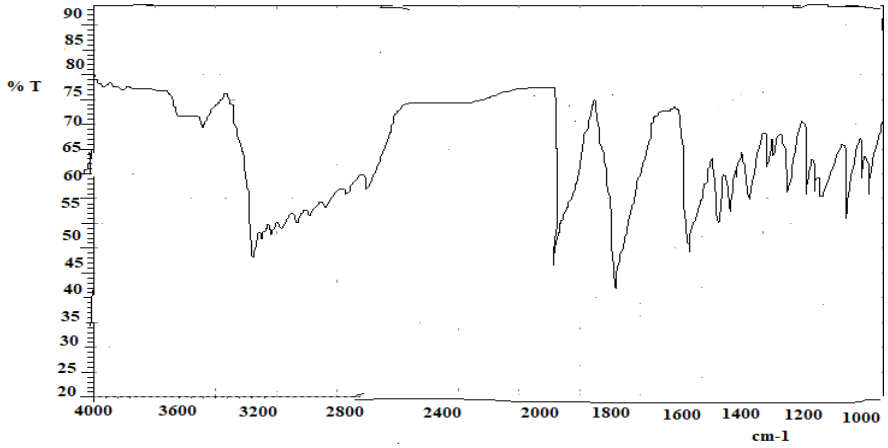

Fig. 2 FTIR spectra of Valsartan

Table 4: Interpretation of FTIR spectrum

Sr. No	Wave number (cm^{-1})	Vibrations
1	3456.36	C-H stretching (aliphatic)
2	2345.98	C-H stretching (aromatic)
3	743.2	C-H bending (aromatic)
4	1475.2	N=N Stretching
5	1794.23	C=O Stretching (ketone)
6	1223.0	O-H bending(alcohol)

DSC Analysis

DSC thermogram of valsartan is obtained and compared with thermogram in literatures. It was found similar as that of thermograms in standard literatures.

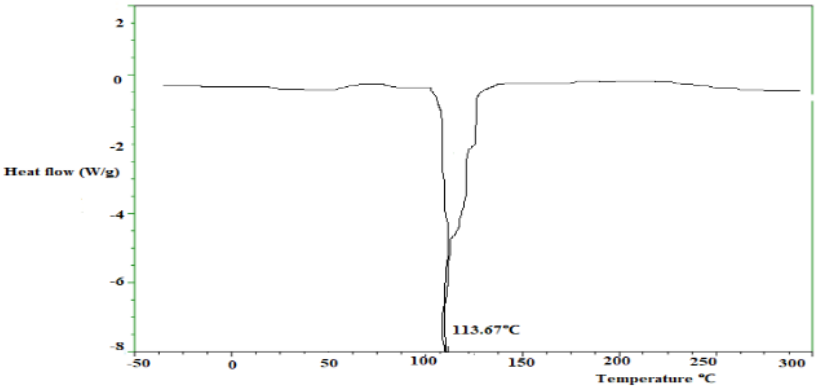

Fig. 3 DSC thermogram of Valsartan

ii) UV spectroscopy, FTIR and DSC of Hydrochlorothiazide

UV Analysis

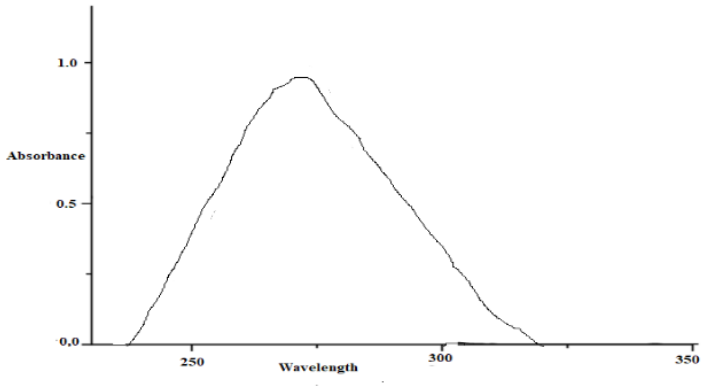

Fig. 4 UV spectra of Hydrochlorothiazide

FTIR Analysis

FTIR analysis of sample of Hydrochlorothiazide API is carried out and it is found that the spectra are similar to the spectra given in standard literatures.

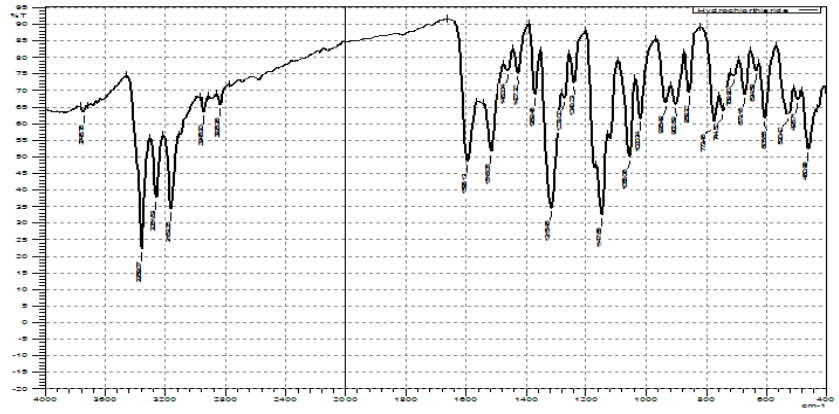

Fig. 5 FTIR spectra of pure Hydrochlorothiazide

Table 5: Interpretation Hydrochlorothiazide FTIR spectra

Sr.no	Wave number(cm^{-1})	Vibrations
1.	3198.63	N-H Stretching
2.	3342.07	O-H Stretching
3.	3195.26	C-H Stretching (aromatic)
4.	2912.3	C-H Stretching (aliphatic)
5.	1601.13	C=C Stretching
6.	1429.32	C=O Stretching
7.	1356.40	C-N Stretching
8.	1398.49	C-H Bending (aliphatic)
9.	1112.65	S=O Stretching
10.	1034.06	C=Cl Stretching

Compatibility of drug and excipient of gastroretentive Mucoadhesive tablet

The FTIR spectra of drug and excipients revealed that there is no considerable alternative in the peak of drugs, and it manifest that there is no interactivity through drug and excipients.

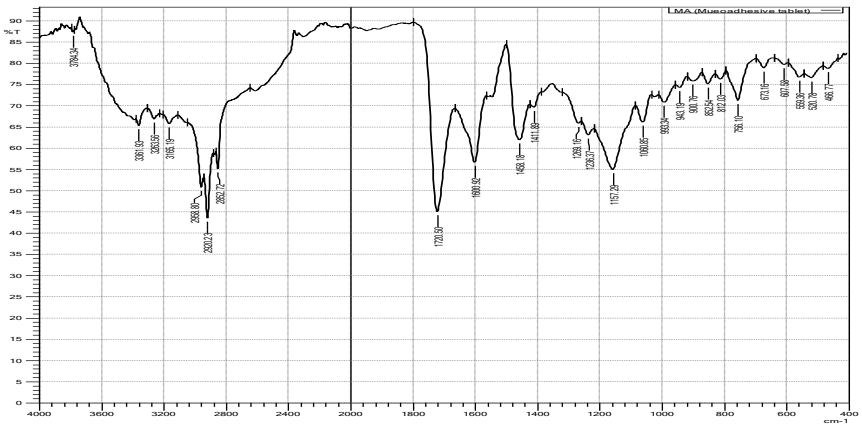

Fig.6: FTIR spectra of drug and excipients gastroretentive Mucoadhesive tablet

DSC Analysis

DSC thermogram of Hydrochlorothiazide is acquired and differentiate among thermogram in literatures. It was established equal as that of thermograms in standard literatures.

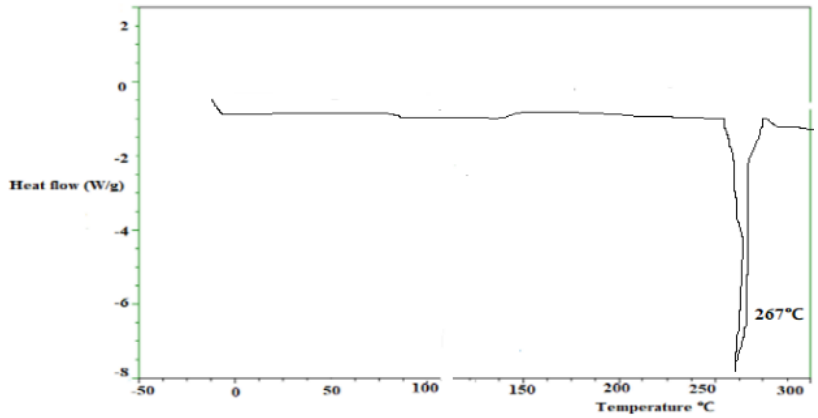

Fig.7: Hydrochlorothiazide DSC thermogram.

Results for assessment of precompression variables of gastroretentive mucoadhesive tablet.

The Valsartan and Hydrochlorothiazide tablet is prepared by direct compression method. The formulated powder blend is assessed before compression during several variables such as bulk density, tapped density, angle of repose, compressibility etc. to check the flow properties of granules and the outcome obtained are as manifest in table 6.

Table 6: Precompression assessment parameter for granules of gastroretentive mucoadhesive tablet

Parameter	F1	F2
Bulk density(gm/ml)	0.51	0.50
Tapped density(gm/ml)	0.62	0.63
Compressibility index (%)	17.74	19.02
Hausner's ratio	1.21	1.26
Angle of repose(degree)	36	38

Results for assessment of Post Compression variables of Gastroretentive mucoadhesive tablets

Formulated Gastroretentive mucoadhesive tablets are assess as per the standard procedures. The evaluations are carried out in triplicates and the outcomes are demonstrated with standard deviations. Results obtained from an evaluation of gastroretentive mucoadhesive tablets are shown in the table 7.

Table 7: Outcome for Evaluation of Post Compression Parameters of gastroretentive mucoadhesive tablet

Parameter	F1	F2
Weight variation(mg)	444.5±0.02	443.6±0.01
Friability (%)	0.36±0.02	0.41±0.03
Hardness(kg/cm^2)	7.6±0.04	7.95±0.03
Thickness(mm)	4.05±0.04	3.95±0.06
Ex-Vivo Mucoadhesion time (hrs.)	9.35	12
Drug Content of Valsartan (%)	98.96±0.4	99.48±0.2
Drug Content of Hydrochlorothiazide (%)	99.26±0.4	99.46±0.2

In-Vitro drug release of Gastroretentive mucoadhesive tablet

In-vitro drug release study performed by employing USP type II (paddle type) dissolution equipment. The study is performed for 8 hrs. at 37±0.5^{0}C and 50rpm by employ 0.1N HCl as dissolution medium. The study is carried on six tablets from each batch. The samples were analyzed on UV

spectrophotometer. The dissolution study is reported as %drug release. The outcome acquired are as showed in table 8.

Table 8: Drug release outline of gastroretentive mucoadhesive tablet

Time(min)	% Drug Release			
	F1		F2	
	Valsartan	Hydrochlorothiazide	Valsartan	Hydrochlorothiazide
0	0	0	0	0
15	5.17 ±0.16	10.69±0.24	11.13±0.24	12.64±0.14
30	10.23±0.63	12.12±0.26	13.25±0.64	14.26±0.18
45	16.12±0.26	16.96±0.31	15.20±0.62	16.25±1.24
60	22.64±0.46	21.44±0.24	18.31±0.34	18.92±0.26
90	30.12±0.06	27.75±0.42	25.06±0.46	24.25±0.08
120	38.26±0.82	36.16±0.28	31.12±0.14	28.04±0.68
150	46.53±1.02	44.25±0.42	37.21±0.46	35.12±1.04
180	55.38±1.03	51.68±0.68	44.32±0.14	39.75±0.38
210	62.22±1.01	56.35±0.22	53.12±0.18	44.24±1.03
240	71.52±0.48	74.59±0.54	61.26±0.41	49.12±0.45
270	86.37±1.69	85.76±0.28	68.04±0.42	53.12±0.68
300	91.38±0.86	87.34±0.14	75.16±0.12	59.16±1.06
360	95.44±1.24	89.22±0.62	83.12±0.42	64.20±0.20
390	97.22±0.62	92.45±0.42	86.03±0.36	68.94±0.92
420	98.44±0.42	94.46±0.64	90.26±0.46	74.03±0.81
450	99.01±0.06	95.44±0.29	91.52±0.84	79.21±0.64
480	99.68±0.18	96.02±0.28	92.31±0.12	85.22±0.48

Accelerated stability studies

According to the ICH guidelines the accelerated stability studies were carried out. Optimized composition F1 were fill in amber colors bottle and aluminium foil overlay on the elevated bit of the bottle and these filled formulation where accumulate in ICH corroborate stability chambers. During 3 months assert at 41^0C ± 3^0C and 74 % RH ± 4 % (zone III situation as per ICH Guidelines). For alternate in emergence, the drug content and in-vitro release the tablets were assessed before and after one month. The samples were noticed during some modification on emergence after a period of one month. It was noticed that tablet was free from of some modification in colors or emergence of some variety of spot on it. It was additionally prominent that tablet was unoccupied of some variety of microbial or fungal growth or bad odour. The preparation batch manifest round shape

among no splits. The drug content of the F1 preparation was established to be 97.91 %, 97.23% and 98.12 % of Valsartan and 98.22%, 98.23% and 99.23% of Hydrochlorothiazide at period of 30 days, 60 days, 90 days sequentially. The %Drug Release of F1 formulation was established to be 98.54% , 98.45% and 99.93% for Valsartan and 97.51%, 96.41%, 97.98% for hydrochlorothiazide at period of 30 days, 60 days, 90 days respectively. The % CDR outcome manifest there was modest reduced in drug content yet variation is inconsequential.

Table no.9: Stability study of Batch F1

Time (days)	Physical appearance	Drug content		% Drug Release	
		Valsartan	Hydrochlorothiazide	Valsartan	Hydrochlorothiazide
30	No change	97.91 %	98.22%	98.54%	97.51 %
60	No change	97.23%	98.23%	98.45%	96.41 %
90	No change	98.12 %	99.23	99.93%	97.98%

Conclusion

In this study conclusion is that the Valsartan and hydrochlorothiazide is excellent coalescence of antihypertensive. The gastroretentive drug delivery system is the best perspective for the sustained release of drugs. The several perspectives may be used for the preparation of gastroretentive drug delivery system but in this study prepared the Mucoadhesive gastroretentive tablet. The stability study of optimized batch of mucoadhesive gastroretentive tablets shows that the formulation is stable.

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