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ORIGINAL ARTICLE

Formulation And Evaluation of Gastroretentive Mucoadhesive Tablet of Nebivolol HCL by Direct Compression Techniques for Management of Hypertension

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ABSTRACT
Nebivolol hydrochloride (a beta blocker) is already reported for the treatment in hypertension. To prolong gastric residence time (GRT), gastroretentive mucoadhesive tablet of Nebivolol HCl (GMTNH) by direct compression method was designed which was not reported till date. The current research was focused to formulate and evaluate the gastroretentive mucoadhesive drug delivery system (MDDS) of Nebivolol hydrochloride to provide controlled release of drug at the desired site of absorption. The proposed gastroretentive mucoadhesive tablet of Nebivolol HCl was prepared with bioadhesive polymer by direct compression method & evaluated for its drug release profile for 24 hr. Hydroxypropyl methyl cellulose K15M, carbopol 940, magnesium stearate, microcrystalline cellulose PH 102 (MCC PH 102) were used as excipients. Absorbance of Nebivolol hydrochloride was observed at 282 nm.The optimized formulation i.e., NBGT4 with (r^2) value and n value 0.9186 and 0.8845 respectively is found to exhibit diffusion mechanism of drug release. Swelling index (%), drug content(%), ex-vivo mucoadhesive strength(gm) of NBGT4 was found to be 158.18%, 99.15%, and 31.02 gm, respectively. In conclusion, gastroretentive mucoadhesive tablet of Nebivolol HCl using direct compression technique achieved the properties for prolonged effect and can be beneficial for further use in the treatment of hypertension.
***Keyword**: Antihypertensive, prolong release, Nebivolol, beta blocker, mucoadhesive.*

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INTRODUCTION

Hypertension is one of the serious and dangerous ailments which affect the heart, cerebrum, kidney and different infection. Chronic hypertension is characterized by elevation in the pressure of blood vessels. It is a substantial contributor to sudden death worldwide, affecting up to 1 in 4 males and 1 in 5 women in the upper one million category. Hypertension is predicted to affect 1.13 billion people worldwide, with the majority (66%) residing in low and middle-income countries. Nebivolol hydrochloride is a cardioselectivity β-blocker used in the management of hypertension [1].

Gastroretentive mucoadhesive drug delivery system (MDDS) prolong the gastric residence time (GRT) and gastro retentive medication conveyance dose structure is those measurement structure which drug out the gastric home time and discharge the medication for expanded timeframe [2, 3].

Bioadhesive polymers can be insoluble polymers or water soluble that are swellable networks, which are connected together by the cross-linking agents. These polymers have most favorable polarity for sufficient wetting while enough fluidity allowing the mutual penetration as well as mutual adsorption of the polymer

and mucus. Polymers such as hydroxypropyl methyl cellulose K15M and carbopol 940, can beused for fabrication of GMDDS [4].

This work aims to formulate and evaluate gastroretentive MDDS of Nebivolol HCl (NBGT) to provide controlled release of drug at the desired site of absorption which attempts to increase the gastric retention time by improving bioavailability of Nebivolol HCl.

MATERIAL AND METHODS

Materials

Nebivolol Hydrochloride (Lab India Pvt. Ltd, India), hydroxypropyl methylcellulose (HPMC K15M), Carbopol 940 (Hi-Media Pvt. Ltd.), magnesium stearate and microcrystalline cellulose (MCC PH 102) (S.D. Fine Chemical Pvt) were used as mentioned in Table 1.

Methods

Preparation of calibration curve of Nebivolol HCl

The stock solution will be made in concentration range of 20- 100 µg/ml. The standard graph of Nebivolol HCl was plotted by standard samples absorbencies on y- axis and their concentrations on x - axis. Regression coefficient value found to be 0.999 which suggest that it obeys the Beer- Lamberts law. Calibration curve of nebivolol HCl in 0.1N HCl is represented in **Figure 1 and Table 2**.

Drug-excipients compatibility study using FTIR

Drug-excipients interaction was studied using FTIR. There was no incompatibility or interaction was observedin between Nebivolol drug and excipients used in the formulation. FTIR spectrum of Nebivolol HCl and its physical combination of drug and excipients were reported in **Figure 2, 3 and 4**. Characteristic FTIR peaks (cm^{-1}) of Nebivolol HCl were observed at 1072 cm^{-1} (C-O stretching), 774 cm^{-1} (C-F stretching), 1210 cm^{-1} (C-N stretching), 1434 cm^{-1} (C-H bending), 3186 cm^{-1} (N-H stretching). FTIR spectrum showed that there was no alteration in peaks of a drug and polymers..

Preparation of gastroretentive mucoadhesive tablet of Nebivolol HCl (NBGT)

The drug and the excipients were sieved by 30# and mixed geometrically. Finally magnesium stearate was sieved from 60# and added to the blend for lubrication. The change in polymer concentration was adjusted with filler concentration i.e., MCC PH 102. The lubricated blend was directly compressed with 6 mm round shaped standard concave punches at a desired weight of 100 mg, carbopol 940 (20 to 30 mg) and HPMC K15M (20-30 mg), magnesium stearate (1 mg) and microcrystalline cellulose PH 102 (44 mg). All the materials Nebivolol HCl, Carbopol 940, HPMC K15, Magnesium stearate and MCC were blended using hand blender, and 9 formulations of GMDDS of Nebivolol HCl using excipients, up to total weight of 100 mg were prepared. Composition of gestroretentive MDDS of Nebivolol HCl is shown in **Table 3.**

Evaluation of NBGT

Pre-compression parameters of Nebivolol HCl mucoadhesive dosage form including bulk density, tapped density [1], angle of repose, carr's index [5], hausner's ratio, weight variation, hardness, friability, thickness, bioadhesive strength and swelling index [6, 7] of gastroretentive mucoadhesive tablet of Nebivolol HCl (NBGT) were determined by the reported methods.

Ex-vivo mucoadhesive strength of NBGT

Modified physical balancing was used to gauge the produced tablet's mucoadhesive strength. In order to balance the weight of both pans, an additional weight is added with a slide to a customized double beam physical balance in which the left-sided pan has been removed and attached with glass sides. Fresh goat intestinal mucosa was utilized as the membrane; it was purchased from a nearby abattoir, kept in solution during transportation, and moistened with 0.1N HCL. With the aid of a surgical blade, the bottom mucous membrane was divided, and it was then bound with a glass slide using thread. The tablets were now designed to adhere to the wooden object and come into touch with the mucosal membrane [1].

Percent Drug content estimation of NBGT

Crushed 10 tablets from all batches in mortar-pestle and weighed equivalent 25 mg drug dose in volumetric flask (100ml) and dissolved in 0.1 N HCl and filtered.

In-vitro drug release and drug kinetic study of NBGT

Hydrochloric acid (0.1N) was used in an USP type 2 (Paddle type) apparatus used for *in-vitro* dissolution study. Rotations per minute (RPM, 50), was used to maintain the temperature at 35.5 °C. To keep the sink condition constant, 10 ml of aliquots were removed at various time intervals and replaced with the same amount of new dissolving medium. Using a UV spectrophotometer, the aliquots were examined for drug content at a maximum 280 nm wavelength [9]. The drug release and mechanism it follows to release can be determined by matching the data with various release models like Higuchi, Korsmeyer- pappas, zero order and first order plots [1].

Statistical analysis

Mean ± SD was used to express values. For a statistical examination of the mucoadhesive strength of several batches, a post hoc turkey test and a one-way ANOVA were utilized. Statistically noteworthy, Kinet DS 3.0 software was employed for kinetic research [7].

RESULTS AND DISCUSSION

In the formulation and evaluation of gastroretentive mucoadhesive drug delivery system (MDDS) of Nebivolol HCl, Direct compression method was adopted in the preparation of gastroretentive MDDS of Nebivolol HCl, composition of carbopol940, and HPMC K15 as swellable polymer. Effect of polymer was studied by preparing different batches of formulation of swelling matrix tablet as mucoadhessive tablet. The drug at dose of 5 mg was constantly maintained in all the batches of formulation and all the necessary evaluation of pre-compression parameters such as flow property determination, carr's index, angle of repose, bulk density, tapped density hausner's ratio was done. During pre-compression study, the angle of repose (21.25° to 26.71°), bulk density (0.131 to 0.174)g/cm^3, tapped density (0.112 to 0.173)g/cm^3, Hausner's ratio (1.1 to 1.58), and Carr's index (19.32 to 26.31)% were observed and mentioned in Table 4. Post compression studies such as hardness, weight variation, thickness, friability, swelling index, (%) drug content, bioadhesive strength and *in-vitro* drug release study were studied. Results of the post-compression studies of optimized formulations i.e. hardness (5.04±0.18 to 5.51±0.11)kg/cm^2, weight variation (100.1±0.8 to 100.6±1.2) mg, thickness (3.8±0.2) mm, and friability (0.31±0.16 to 0.38±0.16)% were observed and mentioned in Table 5. Drug content (%) (98.65±0.14 to 101.32±0.16)%, bioadhesive strength (20.17±0.2 to 31.02±0.5) gm and swelling index (150.23±0.17 to 159.55±0.16) were observed and mentioned in Table 6. Among all the formulations NBGT4 was found to be optimized batch in terms of extended drug release represented in Table 7. Kinetics of release of drug from the formulation followed zero order kinetics depicted in Table 8.

Table 1: Ingredients of the formulation.

S.No.	Ingredient	Function
1.	HPMC K15	Polymer
2.	Carbopol 940	Provide viscosity
3.	Microcrystalline cellulose PH 102	Filler/Diluent
4.	Magnesium stearate	Lubricant

Table 2: Absorbance readings of Nebivolol HCl in 0.1 N HCl for standard calibration curve.

Concentration(µg/ml)	Absorbance
0	0
10	0.12
20	0.24
30	0.35
40	0.48
50	0.59
60	0.72
80	0.96

Table 3: Compositions for various formulations of Nebivolol HCl mucoadhesive dosage form.

Formulation Code	Drug (mg)	Carbopol 940 (mg)	HPMC K15 (mg)	Magnesium stearate (mg)	MCC PH 102 (mg)
NBGT1	5	30	20	1	44
NBGT2	5	30	20	1	44
NBGT3	5	30	20	1	44
NBGT4	5	25	25	1	44
NBGT5	5	25	25	1	44
NBGT6	5	25	25	1	44
NBGT7	5	20	30	1	44
NBGT8	5	20	30	1	44
NBGT9	5	20	30	1	44

Table 4: Pre-compression parameters of Nebivolol HCl mucoadhesive dosage form.

F. code	Bulk density (g/cc)	Tapped density (g/cc)	Carr's index (%)	Hausner Ratio	Angle of Repose
NBGT1	0.152	0.133	19.32	1.1	26.71
NBGT2	0.163	0.157	20.33	1.17	22.33
NBGT3	0.185	0.171	23.21	1.12	26.12
NBGT4	0.143	0.137	22.51	1.17	24.81
NBGT5	0.162	0.165	22.24	1.21	21.25
NBGT6	0.174	0.121	23.21	1.31	27.24
NBGT7	0.191	0.173	26.31	1.58	22.22
NBGT8	0.143	0.112	23.21	1.16	25.15
NBGT9	0.131	0.122	23.31	1.18	26.02

Table 5: Post-compression parameters of Nebivolol HCl mucoadhesive dosage formulations (NBGT1 to NBGT9).

F. code	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)
NBGT1	100.5±2.5	3.8±0.2	5.51±0.11	0.36±0.13
NBGT2	100.2±1.3	3.8±0.2	5.54±0.12	0.31±0.16
NBGT3	101.1±2.0	3.8±0.2	5.31±0.13	0.38±0.11
NBGT4	100.1±1.5	3.8±0.2	5.04±0.18	0.32±0.19
NBGT5	100.6±1.2	3.8±0.2	5.14±0.11	0.34±0.17
NBGT6	101.5±1.7	3.8±0.2	5.36±0.10	0.38±0.16
NBGT7	101.2±1.8	3.8±0.2	5.25±0.44	0.35±0.17
NBGT8	100.1±0.8	3.8±0.2	5.11±0.27	0.32±0.13
NBGT9	102.2±1.9	3.8±0.2	5.10±0.21	0.34±0.13

Table 6: Post-compression effects on swelling index, %drug content, and bioadhesive strength of Nebivolol HCl mucoadhesive dosage formulations (NBGT1 to NBGT9).

F. code	Swelling Index	Percent Drug content	Bioadhesive strength (gm)
NBGT1	150.23±0.17	99.52±0.26	21.03±0.5
NBGT2	159.55±0.28	99.08±0.18	24.52±0.1
NBGT3	156.17±0.21	99.29±0.98	29.36±0.4
NBGT4	158.18±0.22	99.15±0.15	31.02±0.5
NBGT5	157.62±0.03	98.65±0.14	23.12±0.1
NBGT6	156.71±0.31	99.91±0.32	20.17±0.2
NBGT7	157.58±0.11	99.16±0.44	22.24±0.4
NBGT8	156.59±0.25	99.14±0.08	21.25±0.2
NBGT9	156.25±0.19	101.32±0.16	28.56±0.2

Table 7: *In-vitro* drug release study of the prepared mucoadhesive dosage form of Nebivolol HCl formulations (NBGT1 to NBGT9).

Time (h)	NBGT1	NBGT2	NBGT3	NBGT4	NBGT5	NBGT6	NBGT7	NBGT8	NBGT9
2	3.2	4.3	3.1	2.1	2.5	2.8	3.1	3.5	3.8
4	14.6	14.8	12.2	10.5	11.4	11.1	10.5	12.5	15.4
6	25.3	24.3	23.3	21.4	21.6	20.8	22.2	25.6	28.6
8	40	39.1	37.4	33.6	35.3	32.3	38.7	38.2	42.7
10	46.4	46.2	46.3	41.7	45.5	45.5	44.4	45.9	48.4
12	54.1	56.2	53.1	49.3	52.6	52.2	54.3	52.8	55.3
14	66.2	63.2	61.1	57.3	61.5	62.2	60.6	64.7	68.4
16	72.4	70.2	67.6	60.4	68.4	67.9	68.2	69.5	73.6
18	80.5	79.8	75.4	69.2	75.1	74.6	76.7	76.4	82.7
20	85.1	85.3	82.2	76.5	80.3	82.6	81.4	84.3	88.3
22	90.6	89.3	89.5	84.3	87.4	87.3	88.3	88.3	90.6
24	98.6	98.1	97.1	95.5	96.1	96.9	96.6	97.7	99.7

Table 8: *In-vitro* drug release kinetic study profile of the prepared mucoadhesive dosage form of Nebivolol HCl formulations (NBGT1 to NBGT9).

F. code	Zero order		First order		Higuchi		Korsmeyer Peppas model	
	R2	K0	R2	K1	R2	K (min-1/2)	R2	n
NBGT1	0.8711	0.6188	0.5487	0.0123	0.9722	8.5446	0.9384	0.9571
NBGT2	0.8282	0.5914	0.5182	0.0095	0.9515	8.1618	0.9328	0.9319
NBGT3	0.8457	0.6443	0.471	0.0086	0.9416	9.2681	0.9102	0.8769
NBGT4	0.8577	0.6571	0.478	0.0089	0.9422	9.2722	0.9186	0.8845
NBGT5	0.8321	0.6123	0.465	0.0081	0.9512	9.2612	0.9004	0.8762
NBGT6	0.7876	0.6734	0.5265	0.0111	0.9567	8.2341	0.9244	0.9887
NBGT7	0.7768	0.6699	0.5223	0.0102	0.9549	8.2277	0.9256	0.9891
NBGT8	0.6675	0.6318	0.3871	0.0079	0.8642	9.1999	0.8665	0.8676
NBGT9	0.7598	0.6491	0.4317	0.0084	0.9217	9.1504	0.8938	0.8826

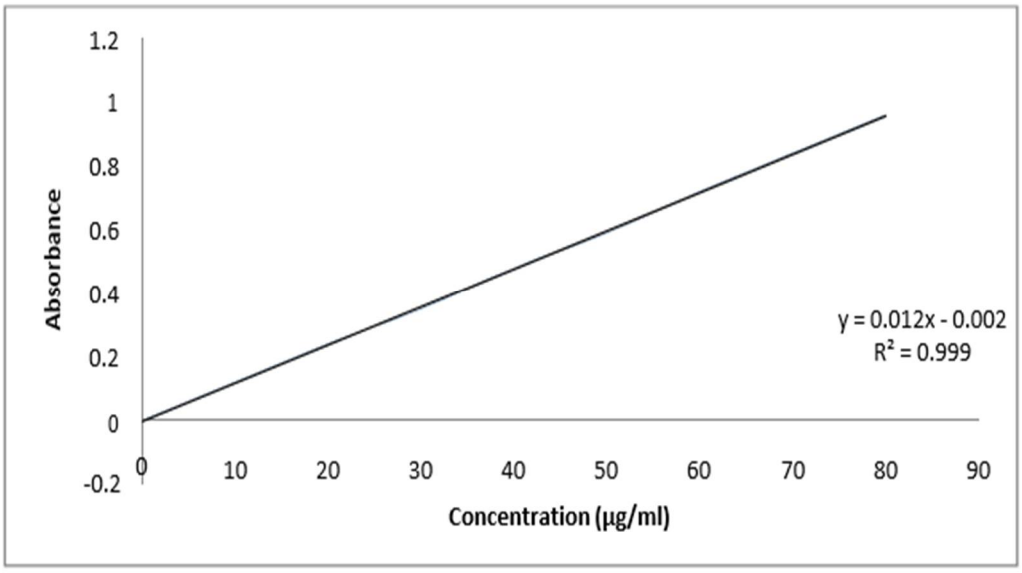

Figure 1: Standard regression curve of Nebivolol in 0.1 N HCL at concentration (20-100 µg/ml).

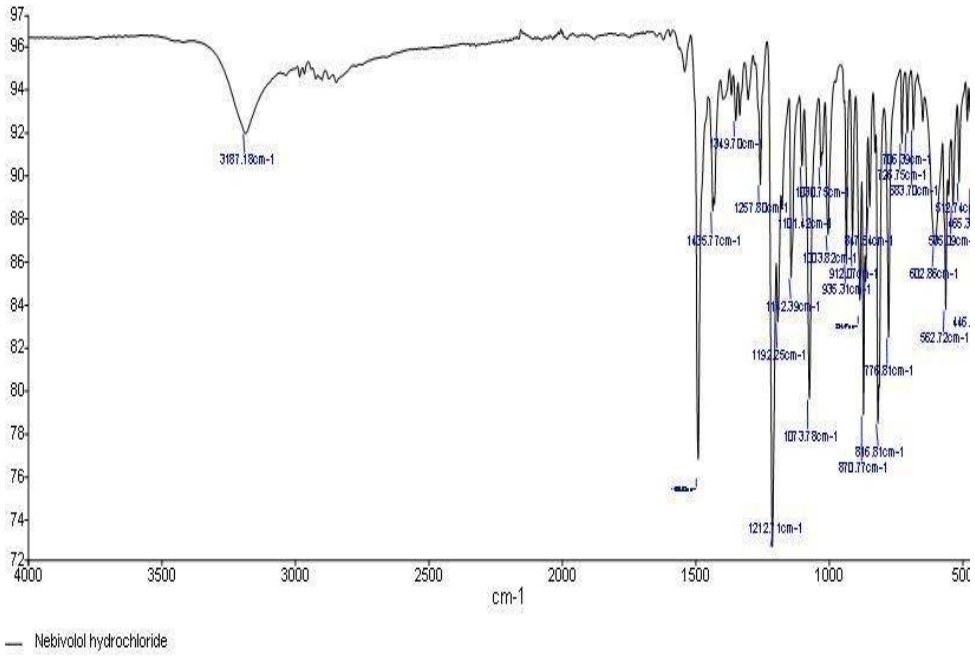

Figure 2: FTIR spectrum of study of pure drug Nebivolol.

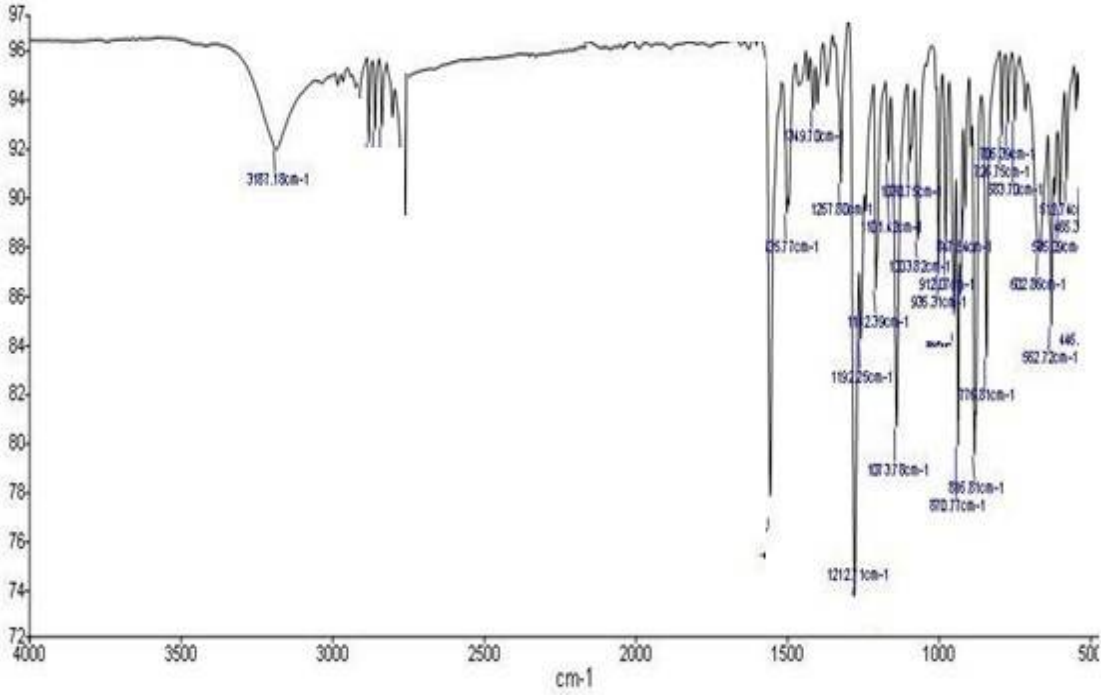

Figure 3: FTIR spectrum of pure drug Nebivolol and excipients

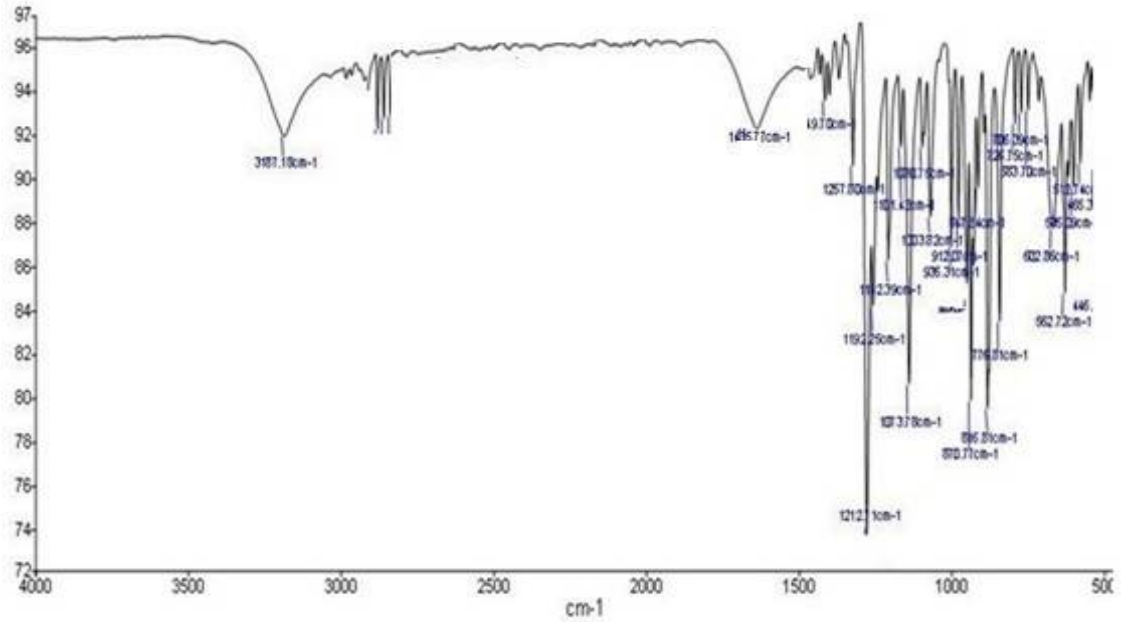

Figure 4: FTIR spectrum of formulation gastroretentive mucoadhesive tablet of Nebivolol.

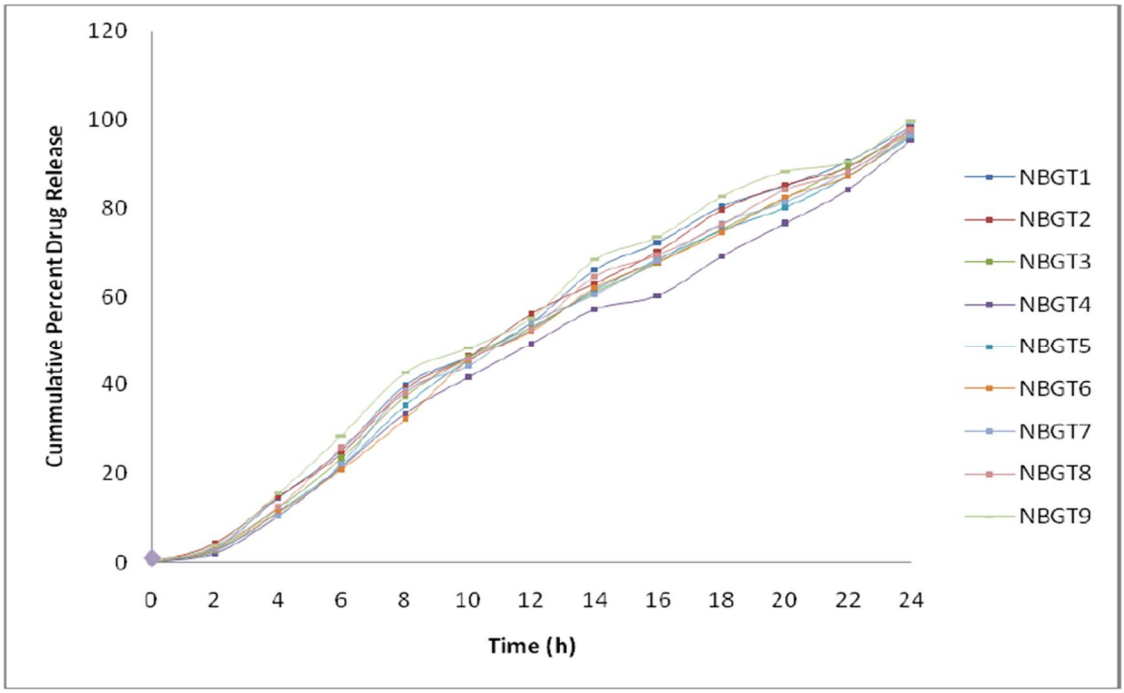

Figure 5: Zero-order kinetic plot of the formulated gastroretentive mucoadhesive tablets of Nebivololin different batches (NBGT1-NBGT9)

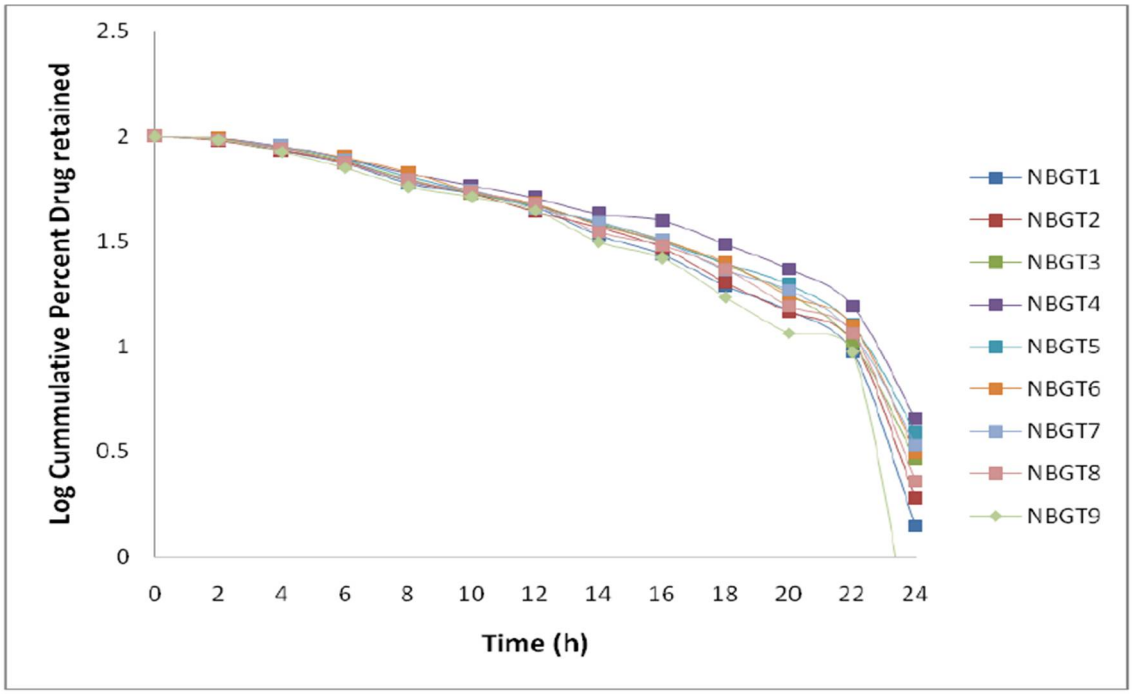

Figure 6: First-order kinetic plot of the forulated gastroretentive mucoadhesive tablets of Nebivolol in different batches (NBGT1 -NBGT9)

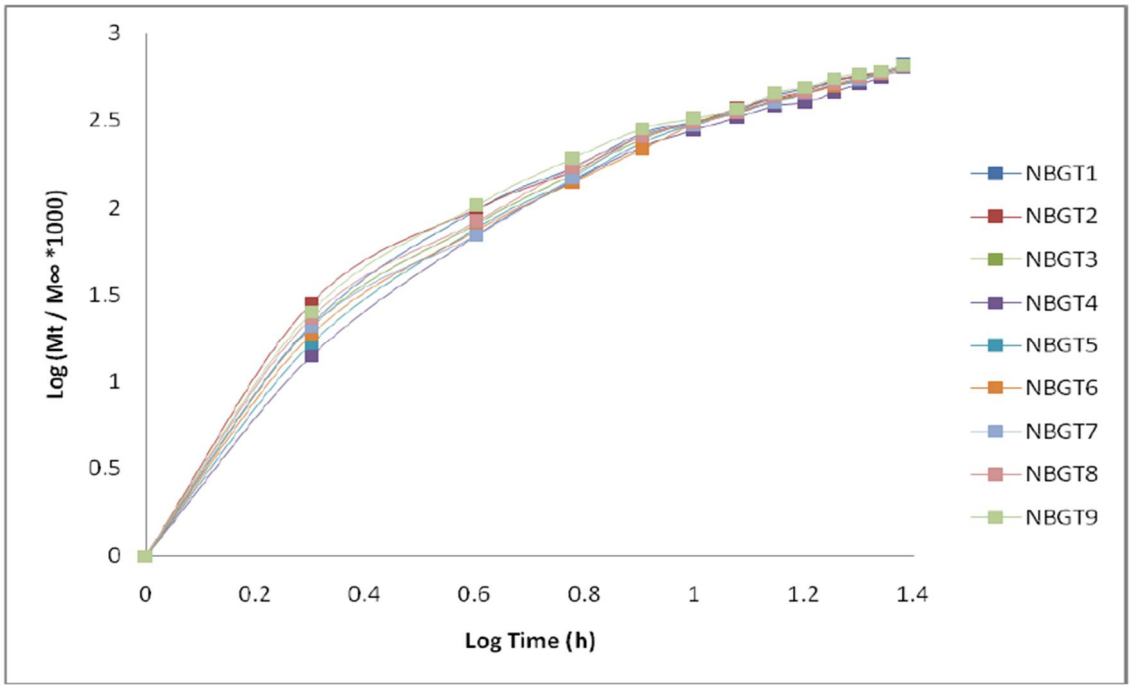

Figure 7: Korsmeyer-peppas kinetic plot of formulated gastroretentive mucoadhesive tablets of nebivolol in different batches (NBGT1-NBGT9).

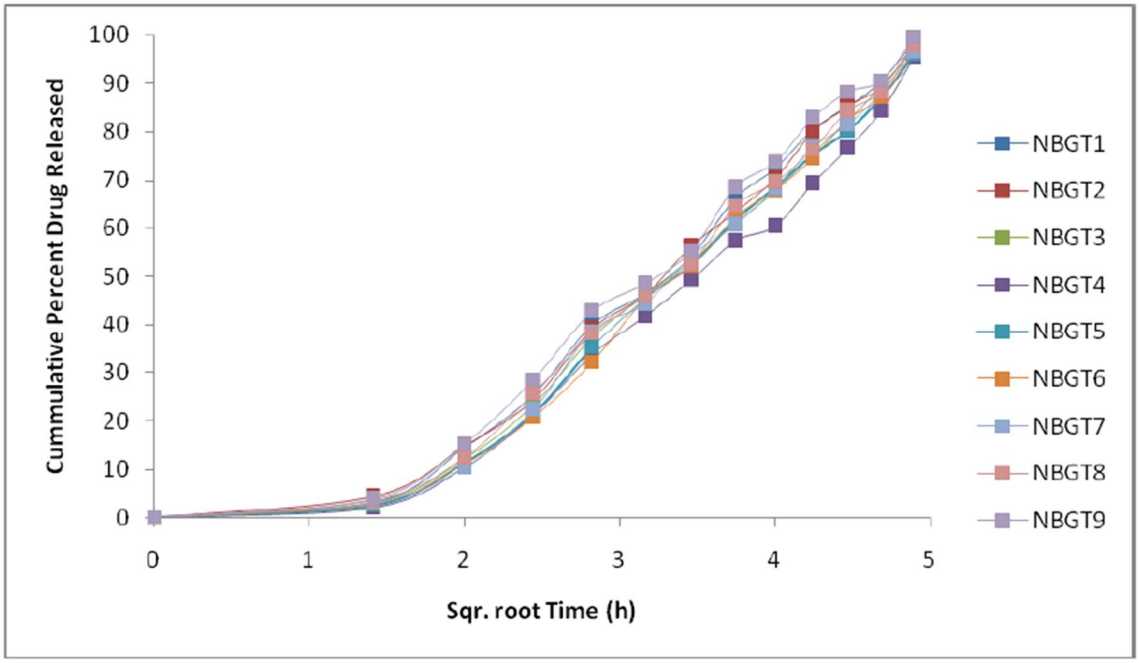

Figure 8: Higuchi kinetic plot of the formulated gastroretentive mucoadhesive tablets of Nebivolol in different batches (NBGT1-NBGT9).

CONCLUSION

In conclusion, the gastroretentive muoadhesive tablet of Nebivolol HCl was formulated and evaluated by several parameters and NBGT4 formulation was found to be optimized among all formulations. It could be beneficial for a prolonged effect in the treatment of hypertension.

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