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Formulation and Evaluation of Gastroretentive Swellable Dosage Forms of Nebivolol HCl

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ABSTRACT

Gastro retentive drug delivery system (GRDDS) is thus beneficial for such drugs by improving their bioavailability, therapeutic efficacy and by possible reduction of dose. Drug absorption in the gastrointestinal tract is a highly variable procedure and it depends upon the factors such as gastric emptying process, gastrointestinal transit time of dosage forms, drug release from the dosage form, and site of absorption of drugs. Nebivolol hydrochloride is a cardioselective adrenergic beta-1 receptor antagonist (beta-blocker) that functions as a vasodilator through the endothelial L-arginine/ nitric oxide system. It is used to manage hypertension and chronic heart failure in elderly patients. Present study aimed towards formulation and evaluation of gastroretentive swellable tablet of Nebivolol HCl by effervescent technique. Prepared tablets were evaluated for various physical properties such as Weight variation, hardness, thickness, friability, drug content and *in-vitro* drug release study. The prepared swellable tablets showed good *in-vitro* dissolution properties. Swelling time showed in the range of 60 to 145 sec. Formulation F6 of Sodium starch glycolate was considered as the best formulation with maximum drug release of 88.38%.

INTRODUCTION

The oral route is preferred for the administration of most of the therapeutic agents due to the low cost, ease of administration and patient compliance. Controlled-release drug delivery system (CRDDS) provides drug release at a predictable, predetermined and controlled rate (1). The important requisite and successful performance of an oral CRDDS is relies continuous drug absorption and retention in stomach (2-3). They can improve the controlled delivery of drugs for continuous release the drug for a prolonged period and increased bioavailability (4). GRDDS divided into four classes: (i) floating systems (5-6), (ii) expandable systems (7), (iii) bio-adhesive systems (8) and (iv) high density systems (9). Floating systems are of two types: (A) effervescent systems, depending on the generation of carbon dioxide gas upon contact with gastric fluids, and (B) non-effervescent systems. The latter systems can be further divided into four sub-types, including hydro-dynamically balanced systems (10), microporous compartment systems (11), alginate beads (12) and hollow microspheres/microballons (13). In addition, super porous hydrogels (14) and magnetic systems (15) were described. As reported (4), the floating drug delivery is of particular interest for drugs which: (a) act locally in the stomach; (b) are primarily absorbed in the stomach; (c) are poorly soluble at an alkaline pH; (d) have a narrow window of absorption; and (e) are unstable in the intestinal or colonic environment. Nebivolol is a novel beta blocker for hypertension. It is widely used to treat hypertension; It has been associated with other diseases and events such as myocardial infarction (MI), heart failure, stroke, and kidney disease. The management of hypertension involves lifestyle modifications, pharmacological treatment, or both. Weight reduction for overweight or obese patients, adherence to the dietary approaches to stop hypertension (DASH) diet, moderate consumption of alcohol, and physical activity are all essential to decreasing blood pressure and enhancing the efficacy of pharmaco-therapeutic regimens. It has less biological half life of and 12% of oral bioavailability (16). Further, the drug has poor aqueous solubility and is soluble in dilute hydrochloric acid (17). Therefore, due to above characters, it becomes a good candidate for the development of GRDDS. The present investigation involved the preparation and *in-vitro* evaluation of nebivolol floating tablets by effervescent technique using a release retarding polymer, polyethylene oxide and a gas former, calcium carbonate (CaCO3). The optimized formulation exhibited excellent floating behaviour, sustained drug release. Further, *in-vivo* investigations were also required to determine mean gastric residence time and bioavailability in healthy human volunteers.

Chavanpatil et al., (2006) prepared a new gastro retentive sustained release delivery system was developed with floating, swellable and bio-adhesive properties. All these properties were optimized and evaluated. Various release retarding polymers like psyllium husk, HPMC K100M and a swelling agent, crospovidone in combinations were tried and optimized to get the release profile for 24 h. Formulations were evaluated for *in-vitro* drug release profile, swelling characteristics and *in-vitro* bioadhesion property. The *in-vitro* drug release followed Higuchi kinetics and the drug release mechanism was found to be of anomalous or non-Fickian type. For the developed formulation, the value of *n* was found to be 0.5766 while for the marketed formulation the value was 0.5718 indicating the anomalous transport (19). Santosh et al: present investigation ideals with the preparation and characterization of swellable drug delivery system (SDDS) of Pregabalin containing Psyllium Husk, HPMC K4M, Crosspovidone and Polyvinylpyrrolidone, as the polymers. The SDDS tablets were prepared by wet granulation method (20). Abeda Aqther et al: Gastro retentive drug delivery systems have shown to be of better significance in controlling release rate for drugs having site specific absorption. Preformulation studies were carried out to optimize the required quantity for HPMC K4M(10%), Eudragit (8%) was used. formulations were prepared using either HPMC k50, HPMC k100, HPMC k4, Xanthan gum, Ethylcellulose with carbopol 934P(21). Muralidhar, et al: Drugs that have narrow absorption window in the gastrointestinal tract (GIT) will have poor absorption. For these drugs, gastro-retentive drug delivery systems offer the advantage in prolonging the gastric emptying time. Swellable, floating, and sustained release tablets are developed by using a combination of hydrophilic polymer (hydroxypropyl methylcellulose), swelling agents (crospovidone, sodium starch glycolate, and croscarmellose sodium) and effervescent substance (sodium bicarbonate). A combination of HPMC K100M, crospovidone, and sodium carbonate shows the good swelling, drug release (22). Gastro retentive delivery systems are retained in the stomach for a longer time and assist in improving the oral controlled delivery of drugs that have an absorption window in the particular region of the GI tract as well as for controlling the release of the drug having site specific absorption limitation.

The aim of this study was to prepare sustained release nebivolol tablets utilizing the gastro-retentive floating drug delivery system by effervescent technique.

MATERIALS AND METHODS

Analytical method: Construction of calibration curve of Nebivolol HCl

An accurately weighed amount of 20 mg nebivolol was transferred into a 100 ml volumetric flask containing 0.1N HCl to dissolve and then the volume was made up to the mark with 0.1N HCl. From this necessary dilutions were made to give concentrations ranging from 1-12 µg/ml solutions. The absorbance of the volumetric solutions was recorded at λ_{max} (220nm) of the drug and plotted graphically to give the standard graph of nebivolol.

Standard Graph Procedure: The study started with the construction of standard calibration curves of nebivolol. The λ_{max} of nebivolol in 0.1N HCl was scanned and found to have the maximum absorbance at 220nm. The standard graph of nebivolol in 0.1N HCl was plotted by taking concentration ranging from 2 to14 µg/mL and a good correlation was obtained with R^2 values of 0.999 respectively.

Formulation development: Preparation of swellable tablets of Nebivolol:

Technology applied: Wet granulation

The key ingredients included in the formulations are:

- Hydrophilic polymers: HPMC K15M, sodium starch glycolate to modify the pattern of drug release from matrix.
- Anti-adherent: Talc
- Lubricant: Magnesium stearate

Procedure: The process simply involves wet massing of the powder blend with a granulating liquid polyvinylpyrrolidone. Accurately weighed quantity of drug nebivolol and polymer such as HPMC K15, sodium starch glycolate is blended and sieved individual material before blending, after blending the granulating liquid polyvinylpyrrolidone was added to prepare wet mass and to prepare granules by passing the wet mass through sieve 22# and absorbed granules were mixed and allowed to compress the tablet using compression machine.

Table 1: Formula used to prepare nebivolol swellable tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6
Nebivolol HCl	20mg	20mg	20mg	20mg	20mg	20mg
HPMC K15	20% (1)	25% (1.25)	30% (1.5)			
Sodium starch glycolate				20 %(1)	25%(1.25)	30%(1.5)
Lactose monohydrate	172.5	62.5	147.5	172.5	62.5	147.5
PVP	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Magnesium stearate (1%)	2.5	2.5	2.5	2.5	2.5	2.5
Talc (2%)	5.0	5.0	5.0	5.0	5.0	5.0

Physical properties of prepared powder blends:

Final Powder Blend: The powder blend of all formulations was evaluated for bulk density, tapped density, compressibility index, Hausner ratio and angle of repose.

Bulk Density: 30gms of material was passed through a sieve no. 25 to break up agglomerates and introduced into a dry 100mL cylinder, without compacting, the powder was carefully leveled without compacting and the unsettled apparent volume, Vo, was read. The bulk density was calculated, in grams per ml, using the formula.

(M)/(Vo)

Where M = Total weight of the powder blend

V_0 = bulk volume of the powder blend

Tapped Density: After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a mechanical tapped density tester that provided a fixed drop of 14±2 mm at a nominal rate of 300 drops per minute. The cylinder was tapped 100 times initially followed by an additional tap of 50 times until difference between succeeding measurement was less than 2% and then tapped volume V_f, was measured to the nearest graduated unit. The tapped density was calculated, in g per ml, using the formula:

(M) / (V_f)

Where M = Total weight of the powder blend

V_f= Tapped volume of the powder blend

Measures of Powder Compressibility: The Compressibility Index and Hausner's Ratio are measures of the propensity of a powder to be compressed. As such, they are measures of the relative importance of inter particulate interactions. As such, they are measures of the relative importance of inter particulate 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 and the Hausner's Ratio, which are calculated using the following formulae:

Compressibility Index = **(Vr-Vo) * 100 / Vr**

Where, Vr = Tapped density;

Vo = Bulk density

Hausner Ratio: It is the ratio of bulk density to tapped density given by the formula

Vo/ Vf

Where, Vo = Bulk density;

Vr= Tapped density

Angle of Repose: The fixed funnel method was employed to measure the repose angle. A funnel was secured with its tip at a given height, H above a graph paper that was placed on a flat horizontal surface. The blend carefully pored through the funnel until the apex of the conical pile just touched the tip of the funnel. The radius, R, of the base of the conical pile, was measured. The angle of repose, α, was calculated using the following formula:

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

Swelling Index: The swelling of the polymers can be measured by their ability to absorb water and swell enormously. The swelling index is the ability of the polymers to swell by absorbing water. The water uptake study of the tablets was carried out by using USP dissolution apparatus type-II. The medium used was 900 ml of distilled water. The testing was carried out at rotation speed of 100 rpm. The temperature of the bath and medium was maintained at 37 ± 0.5ºC throughout the study. The tablets were placed in the medium under rotation. The tablets were withdrawn from the medium after selected time interval, excess water removed by blotting and weighed. The swelling index of the tablets was given by following formula:

$$\text{Swelling Index (\%)} = \frac{\text{Weight of swollen tablet-Initial Weight of Tablet}}{\text{Initial Weight of Tablet}} \times 100$$

***In-vitro* dissolution studies:**

In-vitro dissolution studies were performed for all the batches of swellable dosage forms of nebivolol HCl tablets using USP XXIII dissolution test apparatus –II at 50 rpm, 900 ml of 0.1N HCl used as dissolution media.

RESULTS

Physical properties of prepared powder blends:

The physical properties like bulk density, tapped density, Carr's index (CI), Angle of repose were evaluated for the prepared powdered blend and were calculated and tabulated in table 2

Table 2. Physical properties of powder blends of tablet formulations

Formulation	Bulk density(g/cm3)	Tapped density (g/cm3)	Carr's index (%)	Angle of repose (º)
F1	0.384±0.10	0.454±0.39	14.26±0.54	26.12±0.22
F2	0.389±0.12	0.442±0.76	12.08±0.18	28.36±0.40
F3	0.378±0.14	0.454±0.93	15.02±0.19	25.54±0.19
F4	0.382±0.16	0.453±0.31	14.15±0.19	26.40±0.56
F5	0.402±0.19	0.464±0.54	13.82±0.21	27.92±0.60
F6	0.408±0.12	0.472±0.41	13.71±0.76	30.11±0.05

Evaluation of physical parameters of Nebivolol HCl tablets:

All the prepared formulations were tested for physical parameters like hardness, thickness, weight variation, friability and drug content found to be within the pharmacopeias limits. The results of the tests were shown in the table-3.

Hardness and friability: The hardness of the prepared tablets was found to be in the range of 6.9 to 7.3 kg/cm^2 and is given in table 3. The friability of all the tablets was found to be less than 1% i.e. in the range of 0.21 to 0.26 given in table 3.

Weight variation: All the prepared tablets were evaluated for weight variation and the results are given in table 3. The percent deviation from the average weight was found to be within the prescribed official limits.

Uniformity of drug content: Drug content uniformity in all formulations was calculated and the percent of active ingredient ranged from 95-98% (Table 3).

Table 3: Physical evaluation parameters of tablets

Formulation	Weight variation (mg)	Hardness (kg/cm2)	Thickness (mm)	Friability (%)	Drug Content (%)
F1	249 ±0.21	3.61±0.1	3.78±0.12	0.22±0.11	96.47±1.4
F2	251 ±0.19	3.9±0.1	3.81±0.09	0.25±0.54	95.71±1.5
F3	254 ±0.21	4.1±0.2	3.67±0.75	0.24±0.16	97.44±1.9
F4	255 ±0.19	3.7±0.1	3.75±0.42	0.21±0.12	98.57±1.0
F5	250 ±0.25	4.9±0.1	3.42±0.67	0.24±0.36	97.47±1.6
F6	2 52±0.23	3.8±0.1	3.55±0.45	0.26±0.19	96.27±1.7

Table 4. Swelling time of Gastroretentive swellable tablets of Nebivolol HCl

Formulation	Swelling time in (sec)
F1	354
F2	241
F3	70
F4	60
F5	49
F6	20

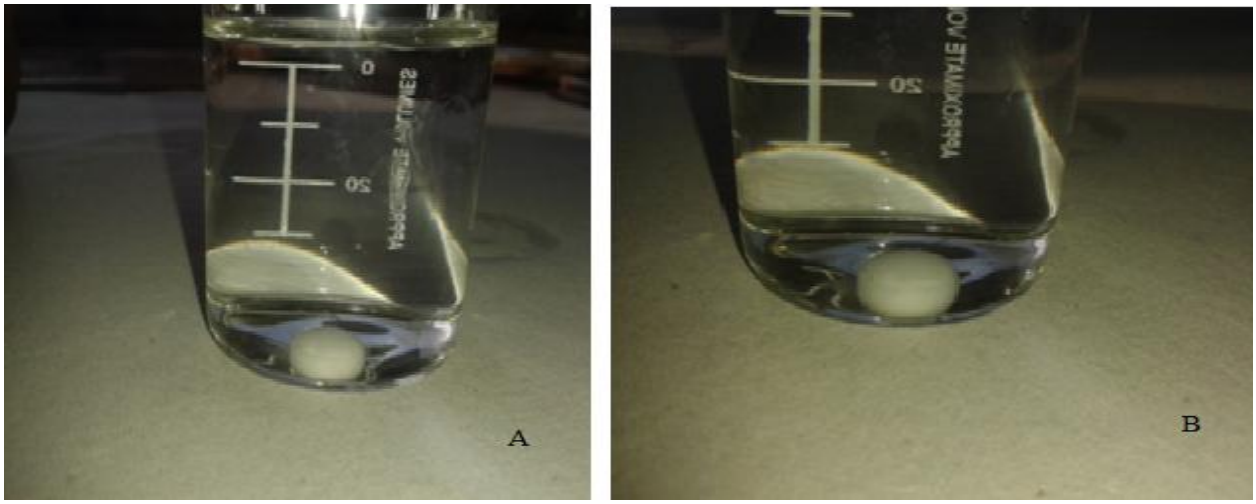

Fig. 1: Gastroretentive swellable tablets of Nebivolol HCl (A) before (B) after swelling

***In-vitro* drug release studies:**

All the formulations (F1-F6) of HPMC K15 and Sodium starch glycolate by varying the percentage of concentration of the polymers were evaluated for the *in-vitro* drug release studies. The results were reported and showed in the following figure 2.

The *in-vitro* drug release studies revealed that formulations showed maximum drug release, 88.38 in 8 hrs. The variation in drug release was due to the different polymer percentages used in the formulation, by using HPMC K15 polymer the cumulative drug release for F1 was 63.7%, F2 was 71.63%, F3 was 77.2% for different percentages and for Sodium starch glycolate the cumulative drug release for F4 was 73.72, F5 was 78.72 and F6 was 88.38. Among all formulation, F6 was considered as best formulation.

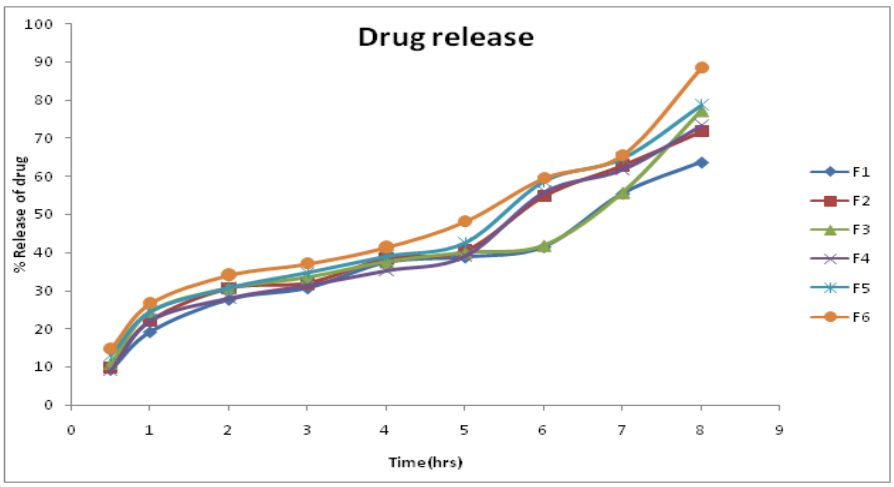

Fig. 2: *In-vitro* drug release of gastroretentive swellable dosage forms of Nebivolol HCl

DISCUSSION

In the present study, gastro-retentive swellable tablet of Nebivolol HCl was prepared by using two different types of polymers like HPMC K15 and Sodium starch glycolate. Excipients like lactose as a diluent and lubricants, and PVP as a binding agent. Tablets were prepared by wet granulation method. The physical properties of the powder blend were evaluated and showed good flow properties. The prepared tablets were evaluated for its hardness, friability, weight variation, drug content, and *in-vitro* dissolution studies (18).

In present work, an attempt was made to prepare of swellable tablets using different polymers of HPMC K15 and Sodium starch glycolate by wet granulation method with Lactose monohydrate as diluents, PVP as binding agent. All the prepared swellable formulations were evaluated for hardness, friability, uniformity of weight, drug content uniformity, swelling index and *in-vitro* drug release studies. The drug-polymer percentage increases the swelling of tablet, to influence the drug release and swelling properties of the prepared nebivolol tablets. Increase in polymer was found to retard the drug release from the dosage form. The prepared swellable nebivolol tablet showed good *in-vitro* dissolution properties. Swelling time showed in the range of 60 to 145 sec. Formulation F6 of Sodium starch glycolate was considered as the best formulation with maximum drug release of 88.38%.

CONCLUSION

Swelling delivery systems offer a simple and practical approach to achieve increased gastric residence and to modify the drug release profiles essential for sustained, site specific and localized drug action. Nebivolol hydrochloride swellable tablets were prepared by using different polymers of HPMC K15M and sodium starch glycolate in different percentages by wet granulation method. PVP was used as binding agent and lactose monohydrate was used as diluents. Finally, it may be concluded that this novel drug delivery system i.e. the gastro-retentive delivery systems offers a valuable dosage form which delivers the drug at a controlled rate and at a specific site. Swelling studies were indicated significant water uptake and contributed in drug release and could be significant in gastro-retention, the swelling provides by allowing a better control of fluctuations observed with conventional dosage forms.

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