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FORMULATION AND *IN-VITRO* CHARACTERIZATION OF NEBIVOLOL PULSATILE DRUG DELIVERY SYSTEM

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ABSTRACT

In majority of individuals blood rises in the early morning hours, which lead to serious cardiovascular complications. Formulation of system makes it possible to deliver drug at definite period of time when symptoms of the disease conditions are most critical. The purpose of the present work was to develop pulsatile release tablet of Nebivolol for chronotherapy in hypertension. The prepared system consisted of a core tablet coated with versatile and safe hydrophilic cellulosic ethers such as, hydroxypropyl methylcellulose, hydroxypropyl cellulose and sodium carboxy methylcellulose to produce brust release after predetermined lag time. Various formulation factors were studied through series of test and in vitro dissolution study. It was found that core tablets containing superdisintegrant failed to produce burst drug release pattern while effervescent agent was able to do so. Results also reveal that coating composition and coating level affects lag time. Formulation containing effervescent agent in core and coated with 200 mg hydroxypropyl cellulose provide lag time of 4.5 h with 96.51% drug release in 8 h that followed a sigmoidal release pattern. These values were close to the desired objective of producing lag time of 3-4 h followed by fast drug release. This approach can thus provide a useful means for timed release of nebivolol and helpful for patients with morning surge.

Keywords: chronotherapy, hypertension, lag time, Nebivolol, pulsatile, sigmoidal, superdisintegrant, cardiovascular, complication, surge.

INTRODUCTION

Pulsatile drug delivery system is defined as the rapid and transient release of certain amount of drug molecules within a short time period immediately after a predetermined off-release period that is lag time[1]. Oral controlled drug delivery systems represent the most popular form of controlled drug delivery system for the more obvious advantage of the oral routes of the administration. Such systems release the drug with constant or variable release rates. These dosage forms offer many advantages, such as nearly constant drug level at the site of action, prevention of peak-valley fluctuations, reduction in dose of drug, reduced dosage frequency, avoidance of side effects, and improved patient compliance However, there are certain conditions for which such a release pattern is not suitable. These conditions demand release of drug after a lag time. In other words, it is required that the drug should not be released at all during the initial phase of dosage form administration. Such a release pattern is known as pulsatile release [2]. The release of the drug as a pulse after a lag time (an interval of no drug release) has to be designed in such a way that a complete and rapid drug release follows the lag time. In chrono pharmacotherapy (timed drug therapy) drug administration is synchronized with biological rhythms to produce maximal therapeutic effect and minimum harm for the patient. By basing drug delivery on circadian patterns of diseases, drug effect can be optimized and side effects can be reduced[3]. If symptoms occur at daytime a conventional dosage form can be administered just prior the symptoms are worsening. If symptoms of a disease became worse during the night or in the early morning the timing of drug administration and nature of the drug delivery system need careful consideration. Pulsatile release is also useful for the targeting of the drug irritating the stomach or degradable therein, as well for drugs developing biological tolerance or with an extensive first-pass metabolism[4]. The first pulsed delivery formulation that released the active substance at a precisely defined time point was developed in the early 1990s. In this context, the aim of the research was to achieve a so-called sigmoidal release pattern.The characteristic feature of the formulation was a defined lag time followed by a drug pulse with the enclosed active quantity being released at once. Thus, the major challenge in the development of pulsatile drug delivery system is to achieve a rapid drug release after the lag time.

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This approach can thus provide a useful means for timed release of Nebivolol and helpful for patients with morning surge [5].

MATERIALS

Nebivolol was obtained as a gift sample from Hema pharmaceuticals Pvt Ltd Ankleshwar, India. Hydroxypropyl methylcellulose K4M (HPMC K4M) and sodium carboxy methylcellulose (NaCMC) was obtained as a gift from Colorcon Asia Private Limited, Goa, India. Hydroxypropyl cellulose (HPC, M.W. 100) was obtained from across organics. All other materials were obtained from SD fine chemical, Mumbai

METHODS

i) Preparation of Nebivolol tablets:

a) Preparation core tablet granules

Two types of core granules were prepared by using effervescent agent and super disintegrating agent. All the excipients except Talc & Mg stearate were sifted through # 40 blended in a poly bag for 10 min.To the above mixture # 60 ASTM passed Talc & Mg stearate were added & lubricated by blending in a poly bag for 5 min.

b) Preparation of Coating tablet granules

Three types of granules were prepared by using three different polymers:i.e. sodium carboxymethyl cellulose (NaCMC) & HPMC K4M.Granules were formed by simple mixing of polymer with 5% w/v alcoholic solution of polyvinyl pyrrolidine K30 to form dough. The formed dough was passed through sieve, dried and re sieved through sieve no. 20. Finally mixed with1% talc and 1% magnesium stearate. In addition to above polymers hydroxypropyl cellulose was directly used (without granulation) for compression coating because of its directly compressible character.

c) Compression of Nebivolol pulsatile release tablets

100 mg of prepared core granules were placed in die cavity to punch core tablet .After that it is collected from punching machine. 200 mg of prepared core granules were weighed and half the amount of granules from 200 mg was filled into the die to form a powder bed. In centre core tablet is placed, over this remaining half of the granules were filled into die cavity. The contents were compressed using concave punches of 10 mm diameter. Hardness of tablet was maintained between 6-8 kg/ cm^2[6].

Table 1: Formulation of Nebivolol Tablet

S. No.	INGREDIENTS	FORMULATIONS					
		F1	F2	F3	F4	F5	F6
1	Core tablet Containing Effervescent Mixture	100	-	100	-	100	-
2	Core tablets Containing Super disintegrant	-	100	-	100	-	100
3	Sodium Carboxymethyl Cellulose granules	200	200	-	-	-	-
4	HPMC K4M granules	-	-	200	200	-	-
5	Hydroxy propyl Cellulose granules	-	-	-	-	200	200
6	Total weight (mg)	300	300	300	300	300	300

EVALUATION

i) Pre Compresion Studies

a) Angle of Repose:

The angle of repose of granules was determined by the funnel method. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.[7]

Tan θ = h/r

Table 2: Pharmacopoeial specifications for angle of repose

Flow Property	Angle of Repose (degrees)
Excellent	25–30
Good	31–35
Passable	41–45
Very poor	>45

b) Bulk Density:

Both lose bulk density (LBD) and taped bulk density (TBD) were determined and calculated by using the following formulas.[8]

LBD = weight of the powder / volume of the powder

TBD = weight of the powder / taped volume of the powder

c) Compressibility Index:

The compressibilty index of the granules was determined by Car's compressibilty index.

Car's index (%) = [TBD-LBD] /TBD X 100

d) Hausner's ratio:

Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following Formula[9]

Hausner's ratio= Dt/Db Where, Dt is the taped density, Db is the bulk density

Table 3: % Comp. Index Properties

5-15	Excelent
12-18	Good
18-21	Fair
23-35	Poor
3-38	Very poor

ii) Post compression parameters

a) Weight variation:

All prepared tablets were evaluated for weight variation. In this twenty tablets of each batch were used to evaluate weight variation among tablets and standard deviation was calculated.[10]

b) Friability:

Friabilty testing was done by Friabilty test aparatus (Lab India Friabilty Aparatus FT 1020).[11]

The percentage friabilty was then calculated by,

% Friabilty = [(W1 – W2) /W1] × 10

% Friabilty of tablets les than 1% is considered acceptable.

c) Hardness:

Hardnes of al batches was determined using tablet hardness tester (Monsanto hardness tester). [12]

d) Thickness:

Thickness was measured by vernier calipers and readings were carried out in triplicate and average value was noted.

e) Drug content:

Twenty tablets were weighed and its average weight was taken which was crushed in motor and pestle. The powder weight equivalent to single tablets i.e. 300 mg was dissolved in 10 mL water in a 100mL volumetric flask and allowed to stand for 10 min. To that 75 mL of methanol was added initally followed by addition of sufficient methanol to produce 100 mL which was then filtered through whattman filter paper. 5 mL of this resulting solution was further diluted to 50 mL with buffer: methanol (1: 1). Again 5 mL was diluted to 50 mL by the same solvent. The absorbance of each of the standard and sample solution were taken in UV-visible spectrophotometer at 276 nm using equal volumes of buffer and methanol as blank [13]

f) *In vitro* drug release studies:

The *In vitro* release of drug from Nebivolol Pulsatile release tablets ware carried out for 8 hours using paddle type tablet dissolution apparatus containing 900 ml of dissolution medium maintained at 37±0.5ºC and speed of agitation at 50 rpm. For the first 2 hours, 0.1N HCl buffer solution was used as dissolution medium and then the dissolution medium was changed by replacing with pH 6.8 phosphate buffer for further 6 hours. At prefixed time interval, 5 ml of solution was withdrawn and analyzed spectrophotometricaly at 276 nm after suitable dilution.[14]

iii) Release Kinetics

The order of drug release from tablet was described by using zero order and first order kinetics.

a) Zero order equation:

This equation describes the systems where the release rate is independent of the concentration of the dissolved species. The dissolution data is fitted into the zero order equation:

Q = Q0. K0t

Where,

Q = Amount of drug released at time t.

Q0 = Amount of drug released initially.

K0 = Zero order rate constant.

A graph of concentration vs. time would yield a straight line with a slope equal to K0 and the intercept at the origin of the axis. The zero order plot is derived from plotting the cumulative percent drug dissolved vs. time.[15].

b) First order equation:

The first order equation describes the release from systems where the dissolution rate is dependent upon the concentration of the dissolving species. Release behaviour generally follows the following first order release equation:

ln M = ln M0 – K1t

Where,

M is the amount of drug undissolved at ime t,

M0 is the amount of drug undissolved at = 0 and

K1 is the corresponding release rate constant.

A graph of log concentration of drug remaining Vs time yields a straight line with a negative slope.

c) Higuchi square root law:

A form of the Higuchi Square Root Law is given by equation

Q = K2 t

1/2 Where, Q = Amount of drug dissolved at time t

K2 = Higuchi rate constant

The Higuchi square root equation describes the release from systems where the solid drug is dispersed in an insoluble matrix, and the rate of drug release is related to the rate of drug diffusion.

d) Korsmeyer- pepas equation:

The Korsmeyer equation which derived from the linear line of log cumulative percentage drug release Vs log time curve is

Mt/ M∞ = Ktn

Where Mt and M∞ are the absolute and the cumulative amount of drug released in time t and infinite time; k is a constant incorporating the structural and geometric characteristics of the device and n is the release exponent which is indicative of the mechanism of release.

This is also known as the power law, if n is equal to 0.89; the release is case I transport. If n is equal to 0.45 the release is best explained by Fickian diffusion, and if 0.45 < n < 0.89 then the release is through anomalous diffusion or non Fickian diffusion.

RESULTS AND DISCUSSION:

a) Evaluation of granules:

The blends prepared for tablets were evaluated for their flow properties. The bulk density and the tapped density for all formulations were found to be almost similar. The Carr's index and Hausner's ratio were found to be in the range of ≤ 18 and 1.0 to 1.23 respectively, indicating good flow and compressibility of the blends. The angle of repose for all the formulations was found to be 11.96 and 12.73˚ which indicating passable flow (i.e. incorporation of glidant will enhance its flow).

b) Evaluation of tablets:

The variation in weight was within the range of ±7.5% complying with pharmacopoeia specifications of USP.The thickness of tablets was found to be between 4.9-5.2 mm. The hardness for different formulations was found to be between 6.6 to 7.3 kg/cm^2, indicating satisfactory mechanical strength.The friability was < 1.0% W/W for all the formulations, which is an indication of good mechanical resistance of the tablet. The drug content was found to be within limits 98 to 102 %.

c) *In vitro* drug release studies:

The *in vitro* dissolution results demonstrate that not all formulations does not show pulsatile release with a distinct lag time. Batch F2, F4 & F6 containing crosspovidone as superdesintegrent in core tablets failed to give proper drug release after lag time. They showed % of drug release 35.48%, 35.47%, 29.03 % respectively. The reason for this is that crospovidone contained within core tablet did not produce requisite extent of internal stress required to exceed the mechanical strength of outer polymeric coat and rupture the coat. Batch F1, F5, F6 showed % of drug release 99.12%, 21.22%, 96.51% respectively. Moreover batches showed different percent of drug release depending on physicochemical properties of the polymer used for coating. From the release profiles depicted in batch F5 can be selected as optimised batch. This is because batch F5 produced lag time of 4.5 h with 96.51% drug release in 8 h. The reason for pulsatile release behaviour by batch F5 is that the internal pressure that is created by the effervescent core is more than the mechanical strength of outer polymeric coat.

Drug release Kinetics:

The mechanism of release for the optimized formulation was determined by fitting dissolution data in to different kinetic models viz. Zero-order, First-order, Higuchi, and Korsmeyer-Pepas corresponding to the release data of formulations. For optimized formulation the R^2 value of zero-order is very near to 1 than the R^2 values of other kinetic models. Thus it can be said that he drug release follows zero-order.

F5 formulation diffusion exponent n value is $0.45 < n > 0.89$ so they are following Anomalous (Non- Fickian) diffusion.

Table 4: Pre compression parameters of Nebivolol core granules

Core granules with	Bulk density (Kg/cm^3)	Tapped density (Kg/cm^3)	Cars index	Hausners ratio	Angle of repose
Effervescent mixture	0.40	0.48	16	1.2	12.73
Super disintegrate	0.39	0.48	18	1.23	11.96

Table 5: Pre compression parameters of Nebivolol coating granules

Formulation Code	Bulk density (Kg/cm^3)	Tapped density (Kg/cm^3)	Cars index	Hausners ratio	Angle of repose (θ)
F1	0.40	0.48	16	1.2	12.73
F2	0.39	0.48	18	1.23	11.96
F3	0.50	0.58	13	1.16	11.58
F4	0.44	0.50	12	1.1	9.92
F5	0.37	0.41	9.75	1.1	12.35
F6	0.36	0.39	7.6	1.0	11.03

Table 6: Post compression parameters of Nebivolol core tablets

Core tablet containing	% weight variation	Thickness ± SD n=3 (mm)	% friability	%Drug Content ± SD n=3	Hardness (Kg/cm^2) Avg wt hardness ± SD n=3
Effervescent mixture	295mg	3.03±0.05	0.132	99.6±1.5	4.63 ±0.057
Super disinegrate	296mg	3.1±0.1	0.133	100.5± 1.4	4.53 ±0.057

Table 7: Post compression parameters of Nebivolol Pulsatile release tablets

Formulation Code	% weight vaiation	Thickness ± SD n=3 (mm)	%*friability	%Drug Content ± SD n=3	Hardness (Kg/cm^2) Avg wt hardness ± SD n=3
F1	295mg	5.03±0.15	0.143	98.9 ±2.3	7.2 ±0.057
F2	297mg	4.93±0.05	0.110	100.2± 1.7	6.7 ±0.1
F3	280mg	5.06±0.11	0.142	101.3 ±1.2	7.56 ±0.057
F4	291mg	5.06±0.15	0.151	102.3 ±1.7	7.03 ±0.115
F5	298mg	5.03±0.057	0.62	100.1 ±1.2	7 ±0.1
F6	292mg	5.1±0.1	0.154	100.7 ±1.1	6.63 ±0.057

Table 8: *In vitro* Drug release data of Nebivolol pulsatile drug Release Tablets

Time (hr)	% of drug release from Core Tablet With Super disintegrate			% of drug release from Core Tablet With Effervescent mixture		
	F2	F4	F6	F1	F3	F5
0	0	0	0	0	0	0
1	4.22	6.32	5.06	10.25	2.22	2.41
2	6.23	9.52	8.44	40.23	3.45	3.21
3	10.21	10.32	19.32	63.25	5.28	5.52
4	11.32	13.2	22.21	83.25	6.15	6.21
5	13.51	15.2	26.72	95.23	8.22	32.34
6	16.89	28.71	27.03	99.12	9.58	55.23
7	25.34	35.47	29.03	99.12	15.23	74.52
8	35.48	35.47	32.03	99.12	21.22	96.51

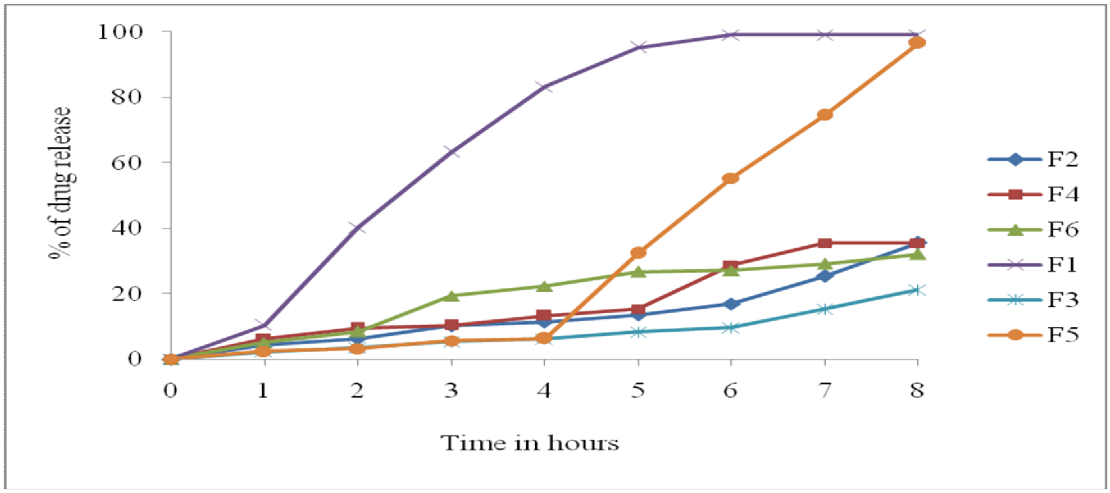

Figure 1: Comparison of Dissolution Profile of all formulations containing Nebivolol pulsatile release tablets (F1-F6)

Table 9: R^2 value and n result table

Formulation code	R square value				n value
	Zero order	First order	Higuchi plot	Pepas plot	
F5	0.899	0.794	0.643	0.843	0.791

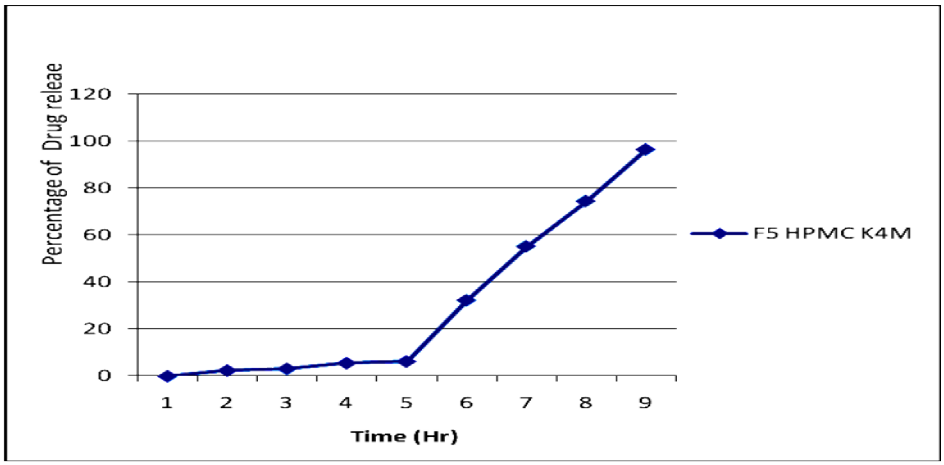

Figure 2: Zero Order Plot For Best Formulation F5

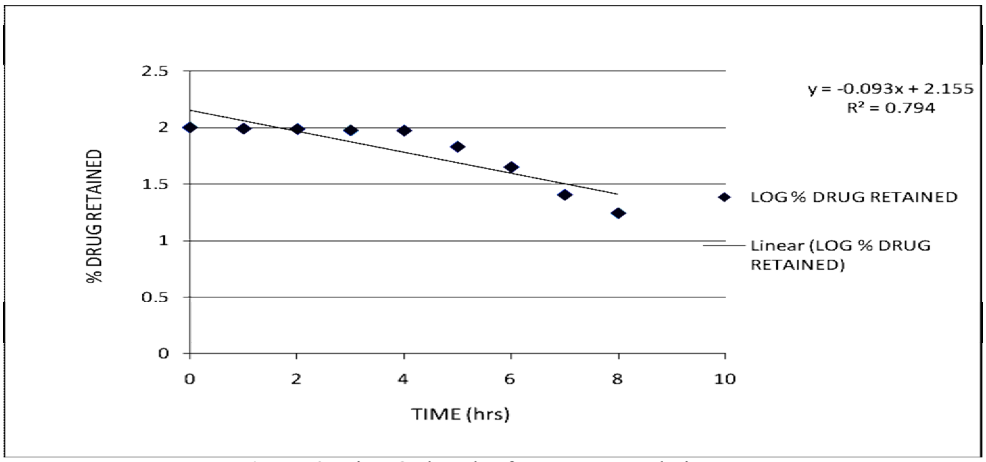

Figure 3: First Order Plot for Best Formulation F5

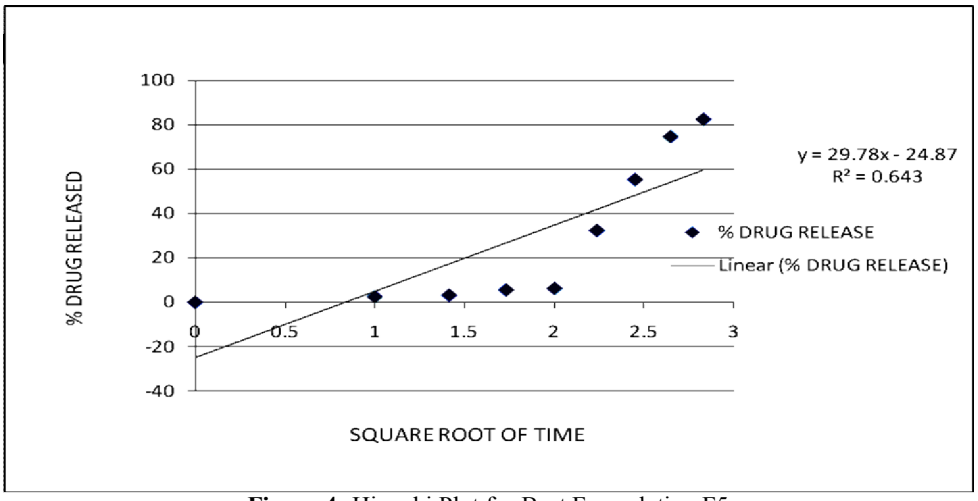

Figure 4: Higuchi Plot for Best Formulation F5

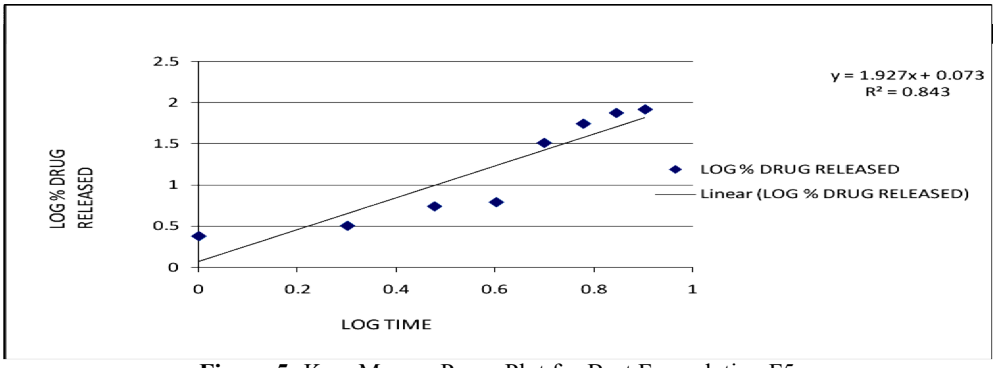

Figure 5: Kors Mayers Pepas Plot for Best Formulation F5

CONCLUSION:

In the present study, to reach an intended release profile, Pulsatile formulation of Nebivolol tablets was developed by using" Tablet in Tablet technique "with different types of polymers. All the prepared tablets were evaluated for various evaluation parameters. From results of the present study clearly indicated a promising lag time that is 4.5 hrs, after that immediate drug release was taken Place (96.5% of drug) in the optimized formulation F5, which contain effervescent mixture in inner core tablet coated with Hydroxy propyl Cellulose. In conclusion, development of Nebivolol pulsatile release tablets could be used for effectively treating hypertension and increasing patient compliance.

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