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FORMULATION DEVELOPMENT AND EVALUATION OF LISINOPRIL SUSTAINED RELEASE TABLETS BY WET GRANULATION TECHNIQUE

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ABSTRACT

The present research was aimed towards developing an oral dosage form having Lisinopril sustained release. Lisinopril is the BCS Class III drug under the Biopharmaceutics Classification System. There are various polymers used in trial-and-error method, among these HPMC and Eudragit and were taken in the ratio 2:5, had successfully retarded the release of Lisinopril for 24hrs in a rate-controlled manner. Hence the present work suggests HPMC as suitable rate retarding polymer for control release formulation of Lisinopril and the study recommends *in vivo* evaluation of the best optimized formula. As per the proto type evaluation results it was concluded that wet granulation is the best possible method of granulation for the present work. Pre-formulation studies were conducted to check the drug polymer and excipients compatibility and the results had confirmed compatibility among them. Granules were evaluated for tests like bulk density, tap density, compressibility index before compression.

KEYWORDS

Lisinopril, Sustained release, Eudragit RSPO, HPMCK100M, Pre-formulation studies and etc.

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INTRODUCTION

The biggest and most established category of drug delivery techniques is oral drug delivery. This is the most popular and rapidly expanding medication delivery method[1-3]. For many years, oral drug delivery systems have been the most widely used method of administration for the systemic distribution of medications through different pharmaceuticals in different dosage forms[4-9].

Products that change the timing and/or rate of medication release are referred to as modified release drugs. The term "characteristics of drug release over time and/or place selected to achieve a therapeutic or functional purpose not achieved by conventional dosage forms such as solutions, ointments, or fast-dissolving dosage forms" refers to modified-release dosage forms. is described as not being offered as it is now acknowledged." Extended or sustained release, avoiding gastric release (enteric coating), targeting various gastrointestinal tract segments (intestinal delivery), and releasing from the stomach are among the benefits[10-16]. Drug selection parameters include stability in the gastrointestinal tract, a half-life of two to eight hours, the absence of substantial first-pass metabolism, and the use of compounds with a high partition coefficient. Better choices for medications that are absorbed into the GIT are those having a lower solubility limit of 0.1mg/ml.

TECHNIQUES FOR PREPARING SUSTAINED RELEASE FORMULATIONS

Based on drug modification

Complex Formation

The dissolution rate of solid complexes in biological fluids and the dissociation rate of complexes in solution are considered and depend on the pH and composition of the gastric and intestinal fluids.

Drug Adsorbent Preparation

Insoluble in this product. Drug availability is determined by absorption rate.

Synthesis of Prodrugs

These are inactive and require enzymatic hydrolysis for refolding. The prodrug's solubility and absorption should be lower than that of the parent drug.

Ion Exchange Resins

These are water-insoluble crosslinked polymers with salt-forming groups. Drugs are bound to resins using chromatographic columns or by prolonged contact. Drug release from this complex depends on the pH and properties of the resin[17-20].

The primary objective of this study is the development and formulation of a solid oral dosage form of Lisinopril at a concentration of 20 mg. The primary objective of this study was the formulation development and evaluation of Lisinopril extended-release tablets by wet granulation. Lisinopril tablets compared to innovative tablets to improve control of plasma drug levels, enhance efficacy and safety, maintain drug concentrations within the therapeutic window, and improve patient compliance[21-26].

MATERIAL AND METHODS UTILIZED

MATERIALS USED

Lisinopril (Madras Pharmaceuticals), Dibasic calcium phosphate dehydrate (Innophos), HPMC K100 M(Qualigen), Eudragit RS PO (Qualigen), Eudragit RL PO (Evonik Degussa), Povidone (ISP, U.S.A), PEG 20,000 (Clarient), Lubritab (JRS pharma), Lactose monohydrate (Rachem ltd), Cross povidone xl 10 (Rachem ltd), Magnesium stearate (Qualigen), Iso propyl alcohol (Rachem ltd), Opadry code (Colorcon) were purchased.

Instruments used

Electrical balance (Well-Tech), Multiple rotary punching machine (Rimek Phase-I), Vernier caliper (Mitutoya), Hardness tester (Monosanto), Friabilator (Nunes), Hydrolic press hardness tester (Dharma scientific products), Dissolution apparatus (Lab India), Sonicator (bath) (Remi equipment pvt Ltd), Dryer (Techno- Tray dryer), Micro centrifugator (Remi Rsearch Centrifugur), Micro syringe, Hot air ovan (Labindian), Bulk density test apparatus (Konark Instruments), Cyclo mixer (Rapid).

METHODOLOGY

Pre-formulation testing is the examination of physical and chemical properties of medicinal products alone and in combination with excipients. This is the first in the rational development of dosage forms. Lisinopril Sustained release tablets were tested by trial and error with both dry and wet granulation, but wet granulation was tested for feasibility. A general evaluation was conducted to validate the granulation technique that can be

changed during product manufacturing so that the final product yields consistent results across test batches. A bioequivalence study was performed using samples from the innovators and was consistent with the drug release studies.

Procedure for Tamsulosin tablet manufacturing by wet granulation method

Accurately weighed quantities of drug and excipients are taken as per standard protocol. The all excipients sieved in #30meshe size then passed in dry mix. These passed materials are blended in RMG for 2 minutes. The binder solution is prepared by dissolving povidone, Lisinoprilin Isopropyl alcohol. The binder solution is slowly added to the dry mix to prepare wet mass. Then the wet mass is kept in tray drier at 45ºC for 1hour.Then the mass was semi passed through sieve number #20 (sieve to bulk mass). Then after drying these granules are passed through sieve number #20. These granules are lubricated with lubricants and if extra granular materials are there. These granules are subjected to compression by using compression machine into tablets. These tablets are coated by using coating solution.

RESULTS AND DISCUSSION

Evaluation of Tablets

The following parameters were performed.

Size and Shape

The size and shape of tablets can be dimensionally described, monitored and control. The compressed tablet's shape and dimensions are determined by the tooling during compression process.

Thickness

The thickness of a tablet was the only dimensional variable related to the process.10 tablets were measured for their thickness and diameter with vernier calipers. Average thickness and diameter were calculated.

Hardness

Tablet hardness has been defined as the force required breaking a tablet in a diametric compression test. To perform this test, there is a Tablet Hardness apparatus. The tablet is placed between two anvils, force is applied to the anvils and the crushing strength that just causes the tablet to break is recorded. Hardness is thus sometimes termed as the tablet crushing strength.

Friability

20 tablets were taken and weighed. After weighing the tablets were placed in the friabilator and subjected to the combined effects of abrasion and shock by utilizing a plastic chamber that revolves at 50 rpm for 4 minutes dropping the tablets from a distance of six inches with each revolution. After operation the tablets were deducted and reweighed.

Dissolution Study

Dissolution Parameters

Medium: 900ml of acid stage medium and followed by pH 6.8 Phosphate buffer + Polysorbate 80 solution

Apparatus : USP Type-II (Paddle)

RPM : 50

Temperature : 37 ± 0.5°C

Time intervals : 1,2,3,4,6,8,12,16,18,20,24Hr

Preparation of acid stage medium

Dissolve 15.0g of sodium chloride in 43.5mL of hydrochloric acid and add water to make up to 10000ml.

Preparation of pH 6.8 Phosphate buffer + Polysorbate 80 solution

Take 5.0ml of Polysorbate 80 into a 1000 ml of pH 6.8 Phosphate buffer + Polysorbate 80 solution and sonicate to dissolve and makeup 10000 ml with volume.

Preparation of diluent

Prepare a mixture of water and acetonitrile in the ratio 70:30.

Preparation of Standard Solution: (Acid stage standard)

Weight accurately about 50mg of Lisinopril working reference standard transfer 100mL volumetric flask add 70ml of diluent, sonicate to dissolve the content and make up to the mark with diluent. Transfer 2ml of above solution into a 50 ml volumetric flask and make upto the mark with acid stage medium. Transfer 2 ml of above solution into a 50ml volumetric flask and make upto the mark with acid stage medium. Filter the solution through 0.45µ membrane filter.

Preparation of Sample Solution

Set the parameters of dissolution apparatus as mentioned above, Transfer the tablets in to an each of the six-dissolution vessel, run the apparatus and immediately. Then withdraw the sample as per the time interval from each dissolution vessel and replace the same volume. Filter the solution through 0.45µ membrane filter.

Procedure

Separately inject 100µL of dissolution media, Five replicate injections of standard solution and single injection of Sample solutions into the chromatograph, record the chromatograms and measure the peak responses.

Pre-formulation Charecterstics of Blend of All Formulations

Pre-formulation study of the Blend - Bulk density, Compressibility index, Tapped density and Hausner's ratio are given in Table No.3.

Table No.1: Standard graph of lisinopril hydrochloride

S.No	Concentration (µg/Ml)	Peak Area
1	0	0
2	20	36782
3	40	73160
4	80	141534
5	120	220216
6	160	293103
7	200	376210
8	240	440213

Table No.2: Results and discussions of the compression parameters

Trail	Thickness (mm)		Hardness (N)		Friability (% w/w)	
	Min	Max	Min	Max	Min	Max
1	3.89	4.11	67.8	80.1	0.52	0.98
2	3.99	4.33	70.4	75.3	0.43	0.86
3	3.87	4.12	61.3	78.6	0.48	0.92
4	3.95	4.23	64.5	79.3	0.55	0.91
5	3.95	2.14	69.9	77.6	0.41	0.89
6	3.96	4.21	68.8	76.9	0.53	0.85
7	3.88	4.28	72.4	79.9	0.42	0.88
8	3.84	4.17	74.8	78.3	0.49	0.94
9	3.87	4.10	71.2	76.4	0.44	0.91
10	3.91	4.29	63.4	75,2	0.59	0.92
11	3.93	4.20	69.5	76.5	0.57	0.90
12	3.81	4.22	63.4	77.1	0.51	0.81

Table No.3: *In-vitro* release profile of lisinopril f1-f6 SR tablets

Time in Hrs	Cumulative Percentage Release of Lisinopril					
	F1	F2	F3	F4	F5	F6
1	3.62	3.82	4.2	4.5	5.9	4.2
2	8.92	7.21	7.63	9.02	11.86	12.36
4	14.23	15.36	16.72	19.83	18.54	19.25
6	21.14	22.12	20.65	29.87	28.68	27.58
8	29.42	34.13	31.96	32.59	38.89	39.96
12	42.67	43.59	53.99	43.9	49.4	53.99
16	59.02	61.90	64.2	57.98	63.89	64.20
18	74.77	77.89	80.32	79.07	81.75	83.76
20	89.97	92.76	91.89	89.41	92.98	93.49
24	95.6	97.23	98.89	94.3	97.52	99.43

Table No.4: Results of pre-formulation study of the blend

Trial	Bulk Density g/cm³	Tapped Density g/cm³	Hausner Ratio	Compressibility Index (%) I=1-V0/V	Angle of Repose (º)
F1	0.56	0.65	1.16	13.84	27.5
F2	0.54	0.63	1.16	14.28	26.8
F3	0.53	0.62	1.15	14.51	26.5
F4	0.52	0.60	1.15	13.5	27.8
F5	0.53	0.61	1.15	13.1	27.6
F6	0.58	0.63	1.14	14.6	26.9

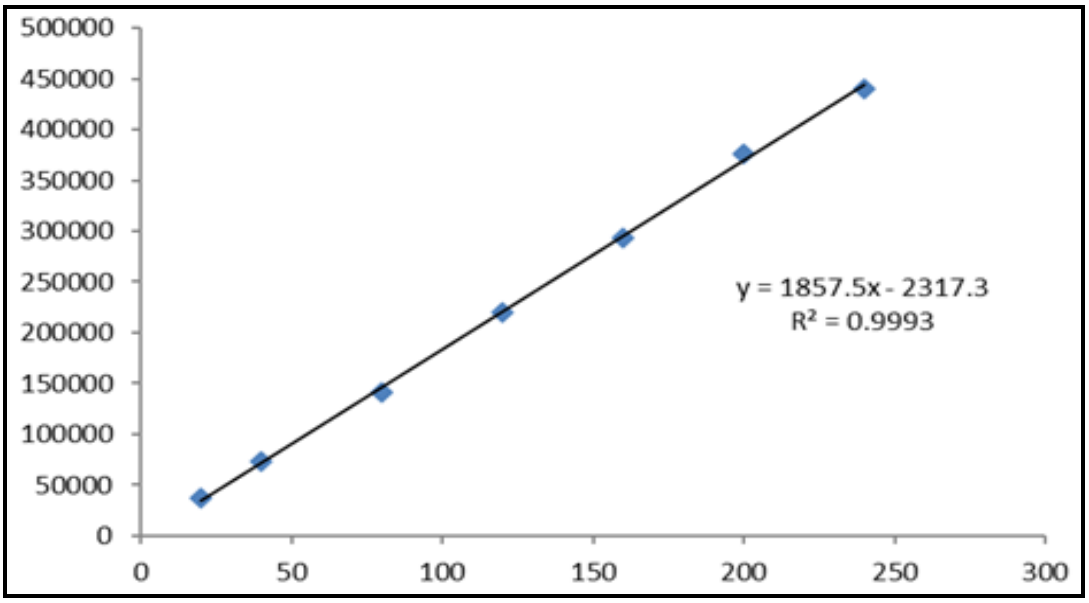

Figure No.1: Calibration curve of lisinopril hydrochloride

SUMMARY AND CONCLUSION

This research work was focused on to develop a sustained release oral dosage form of Lisinopril tablet. As per the proto type evaluation results it was concluded that wet granulation is the best possible method of granulation for the present work. Pre-formulation studies were conducted to check the drug polymer and excipients compatibility and the results had confirmed compatibility among them.

Granules were evaluated for tests like bulk density, tap density, compressibility index before compression. Compressed tablets were tested for *in-vitro* drug release as per the official dissolution procedures. Among all the dissolution profiles it was concluded that trial *F-6* having EudragitRspo and Hpmck100M were taken in the ratio 1:3, had successfully retarded the release of Lisinopril for 24hrs in a rate-controlled manner. Hence the present work suggests HPMCK 100M as suitable rate retarding polymer for control release formulation of Lisinopril and the study recommends in vivo evaluation of the best optimized formula.

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CONFLICT OF INTEREST

The entire author's declared as no conflict of interests.

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