ISSN: 2395-0536

INTERNATIONAL JOURNAL OF PHARMACEUTICAL RESEARCH AND NOVEL SCIENCES

IJPRNS

FABRICATION AND EVALUATION OF CHRONOTHERAPY MODEL OF LERCANIDIPINE HCL: COMPRESSION COATING TECHNIQUE

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ABSTRACT
Aim of this proposal is to design a new chronotherapeutic system for LCH with high potential benefits in treating cardiovascular drugs. The proposed system is a colonic system: A compression coated tablets using chitosan. This new system would benefit from the release in the distal intestinal or the colon, this may exhibit better LCH drug profile comparing a timed-release profile with short lag time of absorption followed by extended higher blood level. This proposed system will be suitable for treatment for cardiovascular diseases with maximum protection against early strokes of the disease. Coating thickness decides the lag time of drug release from the formulation. The order of drug release from the formulations are P3>P6>P5>P1>P4.

Key words: Lercanidipine HCl (LCH), chitosan, chronotherapeutic system

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INTRODUCTION

Hypertension is a chronic disorder and the symptoms of the disease are pronounced predominantly during the early hours of the morning (1). The treatment of this disease condition occurring in the early hours is not convenient by using the existing marketed conventional immediate release dosage form. Hence, a Chronotherapeutic drug delivery system (ChrDDs) with a predetermined lag time may be useful for such patients as the drug is released at a predetermined time and hence the maximum concentration (C_{max}) of the drug can be reached when the symptoms of the disease are worse to fatal. It will be more helpful if antihypertensive patients take the medication before

bed time to overcome a high level of discomfort in the morning (2, 3). It is also thought that ChrDDs may be a successful tool for effective chronopharmacotherapy because of their unique drug release properties, which could take advantage of circadian rhythms in physiologic and pathologic conditions (4). An ideal oral ChrDDs would overcome the problem of administering the drugs frequently. The advantages of ChrDDs include convenience, reduced dosing frequency, reduced toxicity and decreased total required therapeutic or instantaneous preventive drug dose level matching exactly the biological and physiological needs to treat the disease at each point in time. Ultimately, this should lead to improved patient compliance.

Compression-coated tablets (CCT) are dosage forms that consist of an inner core immediate release tablet embedded in an outer layer compartment, which contains either a hydrophilic, hydrophobic or a mixture of both polymers. The outer layer dissolves or disintegrates slowly to release the drug after a predetermined lag time. The advantage of this technique is that it is simply achieved by minor modification of existing equipment, inexpensive, is capable of physically separating two incompatible drugs within the same dosage form, allows taste masking of bitter drugs and is not hazardous to the environment, since it does not require the use of organic solvent (5,6)

Based on literature surey we aim to design a new chronotherapeutic system for LCH with high potential benefits in treating cardiovascular drugs.

MATERIALS AND METHODS

MATERIALS

Lercanidipine HCl (Matrix Laboratories, Hyderabad), CCS (S.D. Fine Chem. Ltd Mumbai), SSG (Sigma Aldrich, USA), MCC, Magnesium sterate (S.D. Fine Chem. LtdMumbai), Talc, Chitosan PVP K 30, PVP K 30 (Merck Pvt. Ltd Mumbai)

METHODS

Preparation of Core Tablets

The core tablets were prepared by direct compression method according to the formula presented. This formula was developed after a number of trials in order to reach an optimum rapid disintegration and dissolution. Initially, amounts of each component equivalent to 20 tablets were weighed. Except for magnesium stearate, they were transferred to a lab scale mixer, allowed for dry mixing for 5 minutes at medium speed. The resulted mass was immediately passed through 22 sieve. The prepared powders were dried in hot air oven at 55°-60°C for half an hour .The dried powder were passed through 12 sieve and lubricated with magnesium stearate for 5 minutes blending, using lab scale double cone blender.The lubricated mixture were compressed using (27 stations) Riddhi pharma rotary tablet press compression machine fitted with 7 mm plain standard concave punches for a tablet weight of 200 mg.

Preparation of Compression-Coated Tablets with Chitosan

Preparation of chitosan granules

Chitosan was granulated by the wet method using 10% (w/w) PVP K30 before using in compression. This was applied based on a previous work done by Yassin, (7) and Shivakumar et al., (8). Simply, 45 g of chitosan low molecular weight were mixed thoroughly with 5 g of PVP K30. Gradually, ethanol 96% was added till the formation of wet cohesive mass. Around 17 ml of ethanol 96% was consumed and granulation time was 5 minutes. The obtained granules were spread over the stainless steel tray and allowed for drying over night at ambient temperature and finally sieved through 22 seive to give uniform granules.

Compression-coating procedures

The produced core tablets from the previous part were subjected to compression-coating with chitosan granules. A single punch rotary compression machine was used fitted with a 12 mm diameter concave punch. Half the amount required for the coat was placed in the die. The core tablet was carefully positioned in the center of the die and then the other half was added. The granules were compressed around the core using constant compression force. This was achieved by adjusting the distance between the upper and lower punches to be constant. Different coat weights were used: 200, 300 and 400 mg per tablet representing, F1, F2 and F3, respectively.All the prepared compression coated tablets were evaluated for the uniformity of coat thickness and the in vitro release characteristics.

RESULTS AND DISCUSSION

The present investigation was aimed to develop novel oral colon targeted compression coated tablet systems of Lercanidipine HCl for safe and effective therapy of hypertension by using chitosan as a coating material. Chitosan proportion ratio is shown in Table-1. The ability of compression coated tablets of Lercanidipine HCl to remain intact in the physiological environment of stomach and small intestine was assessed by conducting in *vitro* drug release studies in 0.1N HCL for 1h and in phosphate buffer pH 7.4 for 1h to assess the ability of the compression coated tablets to release drug in the physiological environment of colon.

Table-1 showing Formulation of coated tablet

Formulation	F3			F6		
	P1 (mg)	P2	P3	P4	P5	P6
Chitosan+ pvp k 30	200	300	400	200	300	400
Ethanol	Qs	Qs	Qs	Qs	qs	Qs

The core tablet has been prepared by using two different disintegrants like SSG, CCS by direct compression with vehicle MCC. All the characteristics of the core tablets including the uniformity of weight and thickness, hardness and disintegration time are performed. It is obvious that the prepared core tablets showed excellent characteristics. The uniformity of dosage form is only expressed by the uniformity of weight for label amounts higher than 25 mg. The mean hardness value was 5 Kgs/cm^2 which is high enough to withstand further coating processes by compression.

The core tablets exhibited a very low friability with only 0.081% in addition, the tablets showed a very fast disintegration time with mean value of 62 seconds. According to the data shown in Table-2, the prepared core tablets exhibited a rapid dissolution in water giving 50% release after only 5 minutes which is considered accepted according to the USP -30-NF25, 2007 criteria and 100% dissolution in less than 45 minutes. From the data two formulations F3,F6 has been selected as good formulations for the coating for further studies.

Table-2 showing % Drug release of core tablet

Time(min)	F1	F2	F3	F4	F5	F6
5	45.11±0.69	47.11±0.50	41.88±0.50	49.45±0.50	43.77±0.50	38.98±0.57
15	74.49±0.69	70.18±0.70	81.46±0.50	69.87±1.01	67.93±0.67	86.99±0.69
30	84.25±0.84	87.62±0.68	97.76±0.61	83.22±0.12	86.23±0.55	96.64±0.65

The compression coated formulae were prepared individually with constant compression force by adjusting a constant distance between the upper and lower punches. This explains the high similarity in the coat thickness among each batch with very low deviation values. The total weight of the coat layer were 200, 300, 400 mg per tablet for P1, P2, and P3, respectively. The uniformity of dosage form is only expressed by the uniformity of weight for label amounts. The mean hardness value was 6.6 Kgs/cm^2 which is high enough to maintain the integrity of the film. The coated tablets exhibited a very low friability with only 0.081%.

Table (3, 4) and Figure (1, 2) represent the release profile of Lercanidipine from six compression coated tablets. Dissolution studies were carried out in pH 1.2 for 1hours, immediately followed by pH 7.4 for 1 hour to simulate the transit times and pH conditions pertaining in the upper gastrointestinal tract. The first acidic hours to represent the average gastric residence time and the next 1 hours at pH 7.4 represents the average intestinal residence time of the dosage form. The results showed a very fast release for P1, this indicates the inability of the chitosan coat at this thickness to retard dissolution. The tablet disintegrated rapidly releasing the drug in P1, P4.On the other hand, at higher coat thicknesses P2, P3, P5 and P6 showed maximum protection for drug release in the acid phase with no release. In the alkaline phase, P2 showed early release of drug at 92.51±0.84 hours followed by markedly higher rate of release in the next hour giving a total amount equal.

Table-3 showing % drug release in 0.1 N HCl

Time(min)	P1	P2	P3	P4	P5	P6
5	0±0	0±0	0±0	0±0	0±0	0±0
15	0±0	0±0	0±0	0±0	0±0	0±0
30	0.2±0	0.4±0.1	0±0	0.4±0.11	0.1±0.1	0±0
60	0.96±0.1	0.54±0.12	0.26±0.56	1.1±0.34	0.6±0.21	0.3±0.2

Table-4 showing % drug release in PBS 7.4

Time(min)	P1	P2	P3	P4	P5	P6
5	45.11±0.69	47.11±0.50	49.45±0.50	41.88±0.50	43.77±0.50	45.55±0.50
15	54.49±0.69	60.18±0.70	65.87±1.01	51.46±0.50	57.93±0.67	61.62±0.67
30	89.53±1.07	70.87±0.69	77.48±0.50	88.99±0.51	69.50±0.83	73.87±0.69
45	78.63±0.66	92.51±0.84	89.05±0.68	75.80±0.51	89.24±0.84	85.86±0.70
60	69.53±1.07	83.64±0.85	95.10±0.50	55.57±0.50	79.25±0.84	93.68±0.52

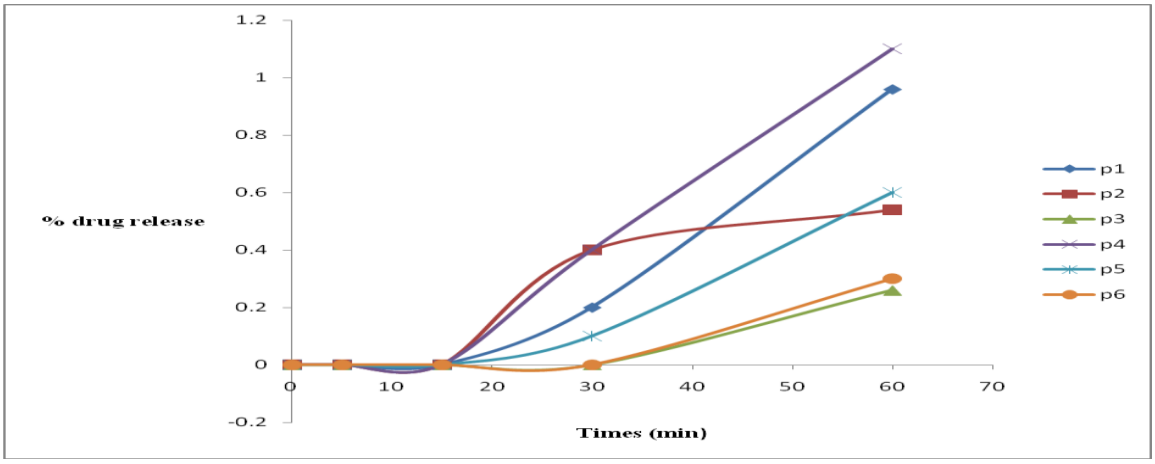

Figure-1 showing % drug release of coated tablet

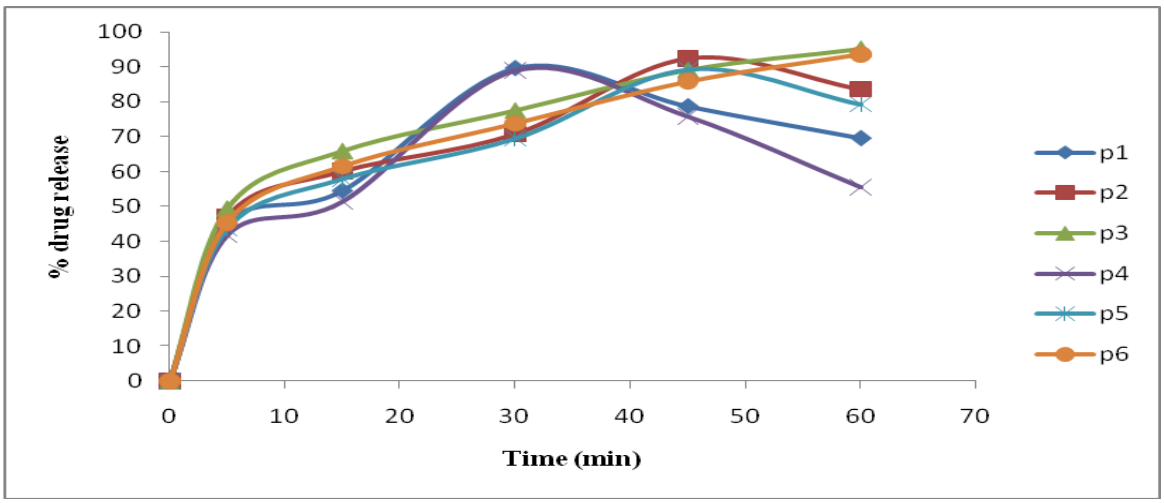

Figure-2 showing % drug release of coated tablet

All of the tested tablets showed the formation of a transparent swelled outer gel layer with inner core clearly seen. The inverse proportionality between the release rate and the coat weight is also reported by in simulated intestinal fluid dissolution.

The mechanism of release postulated that the gel porosity of chitosan allows penetration of salts and enzymes from the media to the core. Thus, the salt will neutralize the gel pH, while enzymes will degrade the polymer which increases the matrix porosity; all these mechanisms tend to enhance the drug release. It is clear that there is a minimum coat thickness necessary for achieving reasonable resistance in the gastro intestinal medium and as the coat thickness increase, the protective properties increase and the variability's diminish.

CONCLUSION

The developed core tablet formula of Lercanidipine HCl showed excellent physical characteristic and high hardness values to withstand further coating processes. The compression coating technique was successful in producing colonic drug delivery tablets embracing number of advantages including: small in size, no need for hardening, cross-linking or film-coating. The successfulness in protecting the coated tablet Lercanidipine HCl from the local environment of the gastro-intestinal medium is highly dependent on the coat thickness. Granulation of chitosan with PVP was very effective in protecting against the effect of the stomach acidic medium on chitosan and obviates the need for further enteric coating. Coating thickness decides the lag time of drug release from the formulation. The order of drug release from the formulations are P3>P6>P5>P1>P4.

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