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FORMULATION AND EVALUATION OF MODIFIED PULSATILE DRUG DELIVERY SYSTEM FOR TELMISARTAN

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ABSTRACT

Telmisartan is an Angiotensin Π receptor antagonist used in the treatment of hypertension. According to the Biopharmaceutical Classification System, Telmisartan belongs class Π drug; high permeability low solubility. It is practically insoluble in water and it shows low dissolution profile and poor absorption. The objective of the present study was to design and evaluate modified pulsatile drug delivery system of marketed product of Telmisartan according to circadian rhythm using natural polymers like xanthan gum, sodium alginate, guar gum, sodium CMC for compressed coated through direct compression method and marketed product of telmisartanas inner core tablet through direct compression method to achieve a predetermined lag time(8hrs) for chronotherapy of hypertension.. Ethylcellulose:HPMC 70mg:130mg(F12), HPMC:Celluloseacetate 130mg:70mg (F15) Xanthan gum: Sodium alginate 75mg: 125mg (F_{20}) and 85mg: 115mg (F21)showed predetermined lag time of 8 hrs so these are selected as optimized formulations and they has shown the immediate release of the drug after the lag time of about 8 hrs. Optimized formulation was evaluated for weight variation, hardness, disintegration time and Invitro dissolution studies, drug – excipient interaction studies.

Key Words: Pulsatile drug delivery system, Telmisartan, marketed product, inner core tablet, xanthan gum, sodium alginate, 8hrs,evaluation, hypertension.

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INTRODUCTION

Compression coating can involve direct compression of both the core and the coat obviating needs for separate coating process and use of coating solutions. The outer tablet of the compression-coated tablet provides the initial dose, rapidly disintegrating in the stomach and the inner layer is formulated with components that are insoluble in gastric media but are released in the intestinal environment. Materials such as hydrophilic cellulose derivates can be used. Compression is easy on laboratory scale. The major drawbacks of the technique are that relatively large amounts of coating materials are needed and it is difficult to position the cores correctly.Press coating also referred to as double compression coating, compression coating (or) dry coating is an old technique first proposed by "Noyes" in an 1896 patent.The technique requires a specific tablet press with compression coating capability.The press coating technique offers many advantages, such as protection of hygroscopic, light sensitive, oxygen liable and acid liable drugs, isolation of incompatible drugs from each other, and provides a method for both sustained drug release and modification of the drug release profile.In general, a press coated tablet consists of an

inner core tablet and an outer coating shell.The outer layer surrounds the inner core, and so selection of outer layer materials has an significant impact on the performance of the tablet, including the coatings mechanical strength, drug release characteristics and tablet stability.The press coating technique has been used to modify the drug release of many drugs, mask of medications bitter taste and protect volatile substances.The press coated tablet may consists of a fast disintegration or modified release core, coated by compression with a solid barrier, commonly made of polymeric material a diluents (as a release modifier) and (for both rapid or extended release).The modified drug release may be dependent on the time, pH or microbial control to target a specific region in gastrointestinal tract.Materials such as hydrophobic, hydrophilic can be used in press coated pulsatile drug delivery systems.Press coated pulsatile formulations release drug after lag time.Press coated drug delivery formulations can be used to separate incompatible drugs from each other to achieve sustained release [1-5].Telmisartan is in the drug class of angiotensin receptor blockers (ARBs) and is prescribed for the treatment of high blood pressure, reducing the risk of heart attack, stroke, or death from cardiovascular causes.Circadian rhythm occurs during blood pressure which is higher during the night than daylight. However the maximal rise in blood pressure occurs early in the morning. Hence the Objective of the present work is to design and evaluate modified pulsatile drug delivery system for Telmisartan according to circadian rhythm using different natural polymers to achieve a predetermined lag time of 8hrs for chronotherapy of hypertension.

RESULTS AND DISCUSSION

Marketed product of Telmisartan was selected as Inner core and evaluation tests such as physiochemical charactarisation, drug content uniformity and disintegration time have been conducted as per the procedure and satisfactory results were obtained and were tabulated inTable-1.

MATERIALS AND METHODS

Designing of Pulsatile Drug Delivery System

Pulsatile drug delivery system was prepared as tablet dosage form which consists of inner core and an outer polymer layer.When the tablet was swallowed, the exposed polymer layer begins to swell. At predetermined time (8hrs) after ingestion, the swollen polymer layer was dissolved and the inner core tablet was then release into colon, where it is dissolved and then absorbed into blood stream. In present study, different polymers are used to prepare pulsatile drug delivery system.

Procedure for Preparation Outer Coat Tablet

Outer coat tablet was prepared by using direct compression method. Weigh required amounts of respective polymers (if in ratios mix them in geometric dilution); now place first layer of polymer and place core at middle and cover the core with final layer. Go for compression using 9mmpunches and dies (if necessary use 12mm) on rotary tablet press keeping varying thickness and hardness values of tablet [6-8].

In-Vitro Release Profile of Compressed Coated Tablet

Dissolution studies were carried out by using USP II dissolution test apparatus (paddle method).900ml of the dissolution medium was used. Rotation speed was 50 rpm and temperature was maintained at $37\pm0.5^{\circ}C$. 5ml of dissolution media was withdrawn at predetermined time intervals and fresh dissolution media was replaced. The withdrawn samples wereanalyzed at 296nm, by UV-visible spectrophotometer and the cumulative percentage release was calculated over the sampling times [9, 10].

Table-1 Evaluation tests for inner core tablet

S.NO	TESTS	CORE (C_2)
1	Thickness	4mm
2	Hardness	$4.16 Kg/cm^2$
3	Friability	0%
4	Weight variation	All tablet passes the test
5	Disintegration time	3.5 mins
6	Drug content	20mg

Based on aim of the project compressed coated tablet with a predetermined lag time of 8hrs was achieved by formula F_{12}, F_{15}, F_{20}, F_{21}. Results obtained for evaluation tests of compressed coated F_{15} tablet were tabulated Table-2.

Table-2 Evaluation Tests of F_{15} Compressed Coated Tablet

S.NO	TESTS	F_{15}
1	Thickness	6mm
2	Hardness	$6.5 Kg/cm^2$
3	Friability	0.12%
4	Weight variation	All tablet passes the test
5	Drug content	20mg

During dissolution studies, it was observed that, the compressed coating is done by using natural polymers, these natural polymers absorbed the surrounding fluid, swelled and release the drug through the swollen matrix.After complete wetting of outer coat, it formed a soft gel like consistency, when it attained a predetermined lag time, which was then easily ejected out of the inner core tablet, releasing the drug in to medium. From the In-vitro drug release studies of device, it was observed that with all formulations there was absolutely no drug release up to lag time. Burst effect was found after lag time and complete drug was release with a time period of 1hr.Formulations F8, F9, F12 are prepared with Ethyl cellulose and HPMC in different concentrations (200mg respectively)depending up on lag timeconducted on different polymers.Formulations F13, F15, F16 are prepared with HPMC Cellulose acetate in different concentrations (200mg respectively). Formulations F20, F21 are prepared with ratios of xanthan gum (56235 -k05)and sodium alginate in different concentrations (200mg respectively). Formulations F23 are prepared with sodium CMC and guar gum in concentrations (325mg:75mg) (Fig-1).
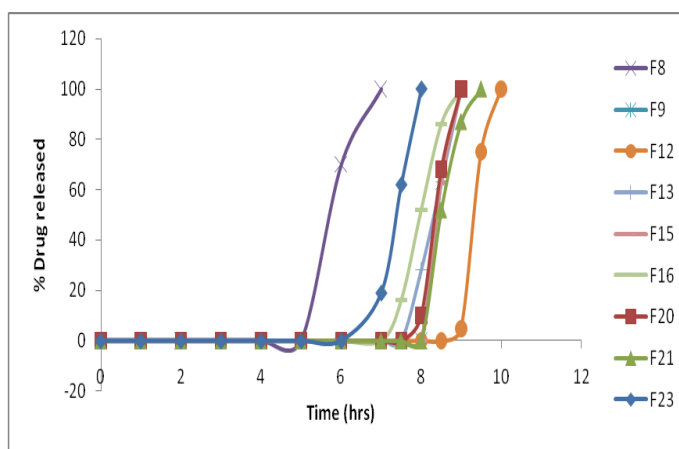

Fig-1 Comparative release profile ofSelected formulations of Telmisartan

CONCLUSION

A successful attempt was made to test effect of different natural polymers on the release of drug from the tablet. Over all 23 pulsatile formulations were made for Telmisartan by using natural polymers. From the dissolution studies carried out on different polymers, the ratio of Ethyl Cellulose and HPMC: Cellulose acetate and HPMC: Xanthan gum and Sodium alginate shows better results. From all the performed in vitro drug release studies, formulation F12,F15,F20,F21 i.e. Ethyl cellulose: HPMC-70mg:130mg , HPMC : Cellulose acetate-130mg:70mg , Xanthane gum: Sodium alginate – 75mg :125mg and 85mg:115mg shows the required lag time of 8hrs and it was selected as optimized formula. Post compression properties like lag time,

drug content uniformity, In-Vitro release profile of pulsatile tablet, Weight variation, Hardness, Thickness, Friability,drug content uniformity were conducted on optimized formulation which has given satisfactory results.Thus designing of proper pulsatile drug delivery will enhances the patient compliance, optimum drug delivery to the target site and minimizes the undesired effects. It should be pointed that these drug delivery systems are still in the early developmental stage and much research will have to be conducted for such systems become practical clinical alternatives. In the present study, a natural polymer based pulsatile drug delivery system with rapid drug release after a predetermined lag time (8 hours) was developed. The optimized batch amongall the formulations showed drug release within 30mints after lag time.The lag time was controlled by natural polymer which will be taken at bed time with a programmed start of drug release early in morning hours. The system was produced with approved excipients and standard processes.

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