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FORMULATION AND EVALUATION OF DILTIAZEM CHRONOTHERAPETIC SYSTEMS BY PRESS COATING TECHNOLOGY EMPLOYING MAGNESIUM STARCH- A NOVEL TIMED-RELEASE POLYMER

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Abstract:

The role of chronotherapeutics in hypertension management is based on the recognition that blood pressure does not remain constant throughout the day. Instead, it tends to be higher in the early morning hours and lower in the evening hours. The main objective of the present studies reported here was to investigate whether compression coating could be used to produce tablets providing maximum In-vitro drug release 8 to 10 hours after an evening dose taken at approximately 6:00 pm– 7.00 pm. The basic idea behind the dosage form development is to investigate effect of novel chronotherapeutic polymer i.e., magnesium starch and coating design on lag time and drug release from directly compressed time-controlled release tablet. The aim of the present study was to design time controlled tablet of Diltiazem hydrochloride, as chronopharmaceutical drug delivery system by press coating employing a novel chronotherapeutic polymer magnesium starch. Coating materials blend were evaluated for micromeritic properties like flow properties, compressibility index, Hausner's ratio and also evaluated the tablet for hardness, thickness, friability and weight variation. The obtained results showed the capability of the system in delaying drug release for a programmable period of time to attain drug release after 10hours after an evening dose taken at according to a time-dependent approach.

Key Words: *Preparation,Diltiazem, Chronotherapeutic Systems, Press Coating Technology, Magnesium Strarch*

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INTRODUCTION:

Chronopharmaceutical drug delivery has been described as a branch of pharmaceutics devoted to the design and evaluation of drug delivery system that release a bioactive agent at a rhythm that ideally matches the biological requirement of a given disease therapy [1]. These systems are beneficial for the drugs having chrono pharmacological behaviour (where night time dosing is required). From the point of view of therapeutic optimization, maintaining a constant blood level for a drug in the human body is questionable. Long-term constant drug concentration exposed in blood and tissues may induce many problems such as tolerance of drug and activation of physiological system. Recently, chronotherapy has been extensively applied in clinical therapy by modulating the dosing regimen of drug administration according to physiological needs [2]. Diseases where in Chronopharmaceutical drug delivery is promising include asthma, peptic ulcer, cardiovascular diseases, arthritis, and hypercholesterolemia [3]. The role of chronotherapeutics in hypertension management is based on the recognition that blood pressure does not remain constant throughout the day. Instead, it tends to be higher in the early morning hours and lower in the evening hours. The widespread use of ambulatory blood pressure monitoring has been instrumental in revealing this pattern of blood pressure variation, which is mediated by the body's diurnal circadian pressure. Sleep pro pensity is mediated by such factors as an increase in melatonin levels and decrease in body temperature and blood pressure [4,5].

The main objective of the present studies reported here was to investigate whether magnesium starch can be used in press coating to produce tablets providing maximum in-vitro drug release 10 hours after an evening dose. The basic idea behind the dosage form development is to investigate effect of core and coating design on lag time and drug release from directly compressed time-controlled release tablet. A dry-coated tablet was recently renewed as a novel system to deliver a drug in a pulsatile way, at predetermined times following oral administration. This novel system is not only rate controlled but is also time controlled. The dry-coated tablets were prepared by a direct compression method. This compression method eliminates the time-consuming and complicated coating or granulation processes and also improves the stability of the drug by protecting it from moisture [6,7]. The purpose of this study was to develop press coated tablets for Chronopharmaceutical drug delivery of diltiazem hydrochloride employing a novel chronotherapeutic polymer magnesium starch. The oral press coated tablet was developed to achieve the time-controlled disintegrating or erodible function with a distinct predetermined lag time

MATERIALS AND METHODS:

Materials:

1. Succinic acid (Finar Chemicals Ltd, Ahmedabad)
2. Sodium hydroxide (Finar Chemicals Ltd, Ahmedabad)
3. Potato starch (Finar Chemicals Ltd, Ahmedabad)
4. Potassium dihydrogen phosphate (Finar Chemicals Ltd, Ahmedabad)
5. Liquid paraffin (Finar Chemicals Ltd, Ahmedabad)
6. Benzene (Finar Chemicals Ltd, Ahmedabad)
7. Potassium bromide (Finar Chemicals Ltd, Ahmedabad)
8. Ethanol (Finar Chemicals Ltd, Ahmedabad)
9. Phenolphthalein indicator (Finar Chemicals Ltd, Ahmedabad)
10. Diltiazem hydrochloride (Yarrow Chemicals, Mumbai)
11. Potassium dihydrogen phosphate (Finar Chemicals Ltd, Ahmedabad)
12. Sodium hydroxide (Finar Chemicals Ltd, Ahmedabad)
13. Hydrochloric acid(Finar Chemicals Ltd, Ahmedabad)
14. Methanol (Finar Chemicals Ltd, Ahmedabad)
15. Diltiazem hydrochloride (Yarrow Chemicals, Mumbai)
16. Crospovidone (Finar Chemicals Ltd, Ahmedabad)
17. Mannitol (Finar Chemicals Ltd, Ahmedabad)
18. Microcrystalline cellulose (Finar Chemicals Ltd, Ahmedabad)
19. Magnesium stearate (Finar Chemicals Ltd, Ahmedabad)
20. Talc (Finar Chemicals Ltd, Ahmedabad)

Methods:

Preparation of Magnesium Starch (A Chronotherapeutic Polymer)

20 grams of potato starch was dispersed in 200ml distilled water to form starch slurry. 12 grams of sodium hydroxide was added to 120 ml distilled water. This solution was added to starch slurry, while mixing, to form a thick gelatinized mass. The mass formed was added to 1200ml of magnesium chloride

(20%w/v) solution contained in a vessel and was stirred at 1200 rpm. The stirring was continued for 1 hour to precipitate magnesium starch form. The magnesium starch formed was collected by vaccum filtration, washed repeatedly with water and dried at 80ºC. Dried polymer was powdered and passed through mesh no 100**.**

Characterization of Magnesium Starch
The magnesium starch prepared was evaluated for the following

Solubility:
Solubility of magnesium starch was tested in water, aqueous buffers of pH 6.8 phosphate buffer.

pH:
The pH of 1% w/v slurry was measured

Melting Point:
Melting point was determined by using melting point apparatus.

Viscosity:
Viscosity of 1% dispersion in water was measured using Ostwald viscometer.

Swelling Index:
Magnesium starch (200mg) was added to 10ml water and light liquid paraffin taken in two different graduated test tubes and mixes. The dispersion in the tubes was allowed to stand for 12h. The volumes of the sediment in the tubes were recorded. The swelling index of the material was calculated as follows.

$$S.I(\%) = \frac{\text{Volume of sediment in water - volume of sediment in light liquid paraffin} \times 100}{\text{Volume of sediment in light liquid paraffin}}$$

Test for Gelling Property:
The gelling property (gelatinization) of the magnesium starch prepared was evaluated by heating a 7% w/v dispersion of each in water at 100ºC for 30min.

Moisture Absorption:
The hygroscopic nature of magnesium starch was evaluated by moisture absorption studies in a closed desiccator at 84% relative humidity and room temperature.

Particle Size:
Particle size analysis was done by sieving using standard sieves.

Density:
Density (g/cc) was determined by liquid displacement method using benzene as liquid.

Bulk Density [8]:
Bulk density (g/cc) was determined by three tap method in a graduated cylinder.

Angle of Repose:
Angle of repose was measured by fixed funnel method.

Compressibility Index (CI)
Compressibility index (CI) was determined by measuring the initial volume (v_o) and final volume(v) after hundred tapings of a sample of magnesium starch in a measuring cylinder. CI was calculated using equation.

Compressibility index (CI) = $V_o - V$

Fourier Transform Infrared (FTIR) Spectroscopy
FTIR spectra of magnesium starch were recorded on samples prepared in potassium bromide (KBr) disks using a bruker FTIR, (Tokyo, Japan). Samples were prepared in (KBr) disks by means of a hydrostatic press at 6-8 tons pressure. The scanning range was 500 to 4000cm^{-1}.

X-Ray Diffraction:
Diffraction pattern of magnesium starch was recorded with an X-ray diffractometer (PanalyticalSpectris Pvt.Ltd., Singapore). X-ray diffraction was performed at room temperature (30ºC) with a diffractometer; target, Cu(λ=1.54Aº), filter, Ni, voltage, 45kV, current 40mA; time constant 10mm/s; scanning rate 2º/min; measured from 10-35º at full scale 20

Drug- Excipient Compatibility Studies
The compatibility of magnesium starch with the selected drug (diltiazem hydrochloride) was evaluated by DSC, FTIR and TLC studies.

Differential Scanning Calorimetry (DSC)
DSC thermograms of diltiazem hydrochloride and their mixtures (1:1) with magnesium starch were recorded on Perkin Elmer analyser. Samples (2-5 mg) were sealed into aluminium pans and scanned at a heating rate of 10ºC min^{-1} over a temperature range 30-350ºC.

Infrared Spectroscopy:[10]
FTIR spectra of diltiazem hydrochloride and their mixtures (1:1) with magnesium starch were recorded on a Perkin Elmer, IR spectrophotometer model: spectrum RXI, using KBr disc as reference.

TLC Study:
TLC was carried out on diltiazem hydrochloride and their mixtures (1:1) with magnesium starch follows;

Stationary Phase:
Silica gel G (pre coated TLC plates)
Mobile Phase:
Glacial Acetic Acid: Water: Methylene Chloride: Anhydrous Ethanol (1: 3: 10: 12)
Procedure:
Mobile phase was prepared and taken in a TLC chamber. The chamber was allowed to saturate with solvent vapour for 24h. Standard (pure drug) and test (drug-magnesium starch mixtures). Samples were spotted on activated silica plates using narrow capillary tubes. The spotted plates were kept in the TLC chamber and allowed to run the mobile phase. The plates were dried and kept in iodine chamber to develop the spots.

Preparation of Diltiazem Hydrochloride Core Tablets:[11]
The inner core tablet was prepared by direct compression method where all the ingredients are weighed accurately and compressed into tablet (average tablet weight is 100mg) using a rotary tablet machine (ShakthiPharma TEC.PVT.LTD.) punch equipped with a 5mm. The core tablets are evaluated for hardness, weight variation, friability and drug content. The core compositions for one tablet are reported in Table 6.1

Characteristics of Core Tablets powder:
Bulk Density:
Bulk density (D_b) was determined by measuring the volume (V_b) of known weighed quantity (W) of granules using bulk density apparatus and can be calculated by using the formula:

$$\text{Bulk density (Db)} = \frac{\text{Bulk volume of powder (Vb)}}{\text{Mass of powder (W)}}$$

Tapped Density:

Tapped density (D_t) was determined by measuring the volume (V_t) of known weighed quantity (W) of granules after desired mechanical tapping using tapped density tester and can be calculated by using the formula:

$$\text{Tapped density (Dt)} = \frac{\text{Mass of powder (W)}}{\text{Tapped volume of powder (Vt)}}$$

Angle of Repose:
The angle of repose of granules was determined by the funnel method. The accurately weighed (10gms) granules were taken in the funnel. The granules were allowed to flowfreely through the funnel on to the surface. Thediameter of the granules cone was measured and angle of repose was calculated using the following equation:

$$\theta = \tan^{-1}\frac{h}{r}$$

Where, θ = angle of repose,
h = height of the cone, and
r = radius of the cone base

Compressibility Index:
Compressibility index (C.I) was determined by measuring the initial volume (V_0) and final volume (V) after 100 tappings of a sample in a measuring cylinder. C.I was calculated by the equation.

$$\text{Compressibility Index (C.I)} = \frac{Vo - V \times 100}{Vo}$$

Drug Content of Core Tablets:
Tablets are finely powdered and quantity of powder equivalent to 10 mg of diltiazem hydrochloride was weighed accurately and transferred into volumetric flask containing 100 ml of phosphate buffer (pH 6.8) and mixed thoroughly. One milliliter of filtrate with suitable dilution was estimated for diltiazem hydrochloride content at 237 nm using double beam spectrophotometer (Analytical Technos 160 UV double beam Spectrophotometer, Mumbai).

Preparation of Press Coated Tablets
The compositions of the coated materials are given in table 2, 3. All the powder mixtures are previously passed through the sieve no. 44. 100 mg of powder mixture was used for the upper and lower shell. The press coating of tablets was performed using a rotary tablet machine (ShakthiPharma TEC.PVT.LTD). A half amount of the powder is filled into the die to make a powder bed, in the center of which core tablet was placed manually. Then, the remaining half of the coating material filled in the die, and the contents were compressed under sufficient compression force, using a flat punch 10 mm in diameter.

Table 1: Core Compositions with Varying Concentrations

Ingredients (mg/tablet)	F1	F2	F3	F4	F5
Diltiazem Hydrochloride	30	30	30	30	30
Crospovidone	2	4	6	8	10
Mannitol	14	12	10	8	6
MCC	50	50	50	50	50
Magnesium Stearate	2	2	2	2	2
Talc	2	2	2	2	2
Total weighing (mg)	100	100	100	100	100

Table 2: Coat Compositions with Varying Concentrations Employing Eudragit-L 100 as Chronotherapeutic Polymer

Formulation		Coating Material (100mg)	Percent Ratio	Amount used in Upper and Lower Shell (mg)
Code	Core Tablet			
DE1	F5	Eudragit-L100:HPMC K-15M	100:0	100
DE2	F5	Eudragit-L100:HPMC K-15M	75:25	100
DE3	F5	Eudragit-L100:HPMC K-15M	50:50	100
DE4	F5	Eudragit-L100:HPMC K-15M	25:75	100
DE5	F5	Eudragit-L100:HPMC K-15M	0:100	100

Table 3: Coat Compositions with Varying Concentrations Employing Magnesium Starch as Chronotherapeutic Polymer

Formulation		Coating Material (100mg)	Percent Ratio	Amount used in Upper and Lower Shell (mg)
Code	Core Tablet			
DM1	F5	Magnesium starch:HPMC K-15M	100:0	100
DM2	F5	Magnesium starch:HPMC K-15M	75:25	100
DM3	F5	Magnesium starch:HPMC K-15M	50:50	100
DM4	F5	Magnesium starch:HPMC K-15M	25:75	100
DM5	F5	Magnesium starch:HPMC K-15M	0:100	100

Evaluation of Core and Press Coated Tablets

The above core and press coated tablet are evaluated for the physical properties like weight variation, hardness, friability.

Hardness:

The tablet hardness, which is the force required to break a tablet in a diametric compression force. The hardness tester in the study was Monsanto hardness tester, which applies force to the tablet diametrically with the help of an in built spring and expressed in kg/cm.

Weight Variation:

To study weight variation twenty tablets of the formulation were weighed using a digital balance and the test was performed according to the official method. The specification for weight variation of tablets as per USP was mentioned in Table 6. Twenty tablets were selected randomly and weighed individually to check for weight variation.

Specification for Weight Variation of Tablets as per USP

Average Weight of Tablets (mg)	Percentage Difference
130 or less	10
130–324	7.5
>324	5

Friability:

The friability of tablets was determined using Roche Friabilator. It is expressed in percentage (%). Ten tablets were initially weighed and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes. The tablets were weighed again. The % friability was then calculated by:

$$\text{Friability} = \frac{\text{Initial weight} - \text{Final Weight}}{\text{Initial Weight}} \times 100$$

Friability of tablets less than 1% are considered acceptable.

***In-vitro* Dissolution Studies of Core and Press Coated Tablets**

The dissolution test core tablet was performed in triplicate using a eight-station USP type II (paddle) apparatus (model-Electro lab, India) at 37°C ± 0.5°C and 50 rpm speed. The dissolution studies were carried out in 0.1 N HCl for 2 hours and later continued with phosphate buffer pH 6.8 upto 10 hours. At every five minutes interval samples of 5 ml were withdrawn from dissolution medium and replaced with fresh medium

Assayed for the amount of diltiazem hydrochloride released by a spectrophotometer (Analytical Technos 160 UV Double Beam Spectrophotometer, Mumbai) at a wavelength of 237nm and 202nm respectively for 0.1N HCl and pH 6.8 phosphate buffer. The amounts of drug present in the samples were calculated with the help of appropriate calibration curve constructed from reference standard.

RESULTS AND DISCUSSION:

The magnesium starch prepared was found to be fine, smooth and free flowing crystalline powder. The physical and micrometric properties of the magnesium starch are summarized in table 4.1, it was insoluble in aqueous solvents and insoluble in organic solvents tested (methanol, petroleum ether, dichloromethane and chloroform) the pH of 0.1% aqueous dispersion was found to be 3.52.

Magnesium starch exhibited good swelling in water. The swelling index was 60.4 all micrometric properties indicated good flow and compressibility needed for solid dosage from manufacturing. The density of Magnesium starch was found to be 0.9991 g/cc. The FTIR spectrum of starch and magnesium starch is shown in fig: 1, 2. The presence of peaks of absorption 2927.21 cm^{-1} C-H stretching is observed. So from FTIR studies it was concluded that Magnesium starch was formed when starch reacted with Magnesium chloride. The X-ray diffraction pattern (fig .3) of starch showed characteristic peaks, which indicates that the structure is completely crystalline.

As the Magnesium starch was crystalline, smooth and free flowing powder and it had got all the characteristics of chronotherapeutic polymer. Therefore, it was concluded that magnesium starch can be used as chronotherapeutic polymer in the formulation of chronotherapeutic drug delivery systems.

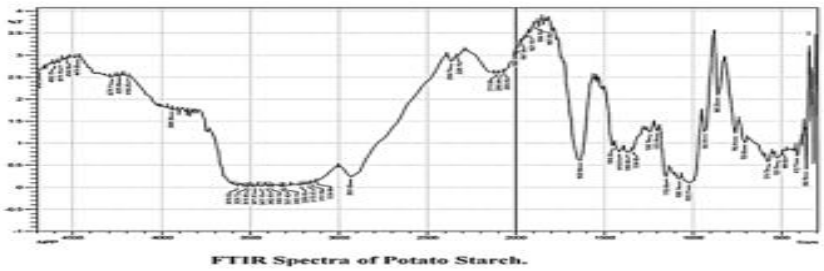

Fig .1: FTIR of Potato Starch

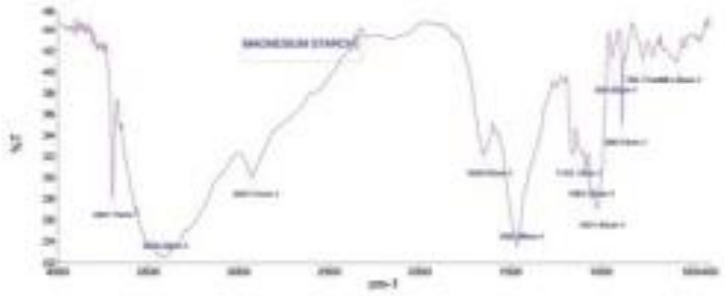

Fig .2: FTIR of Magnesium Starch

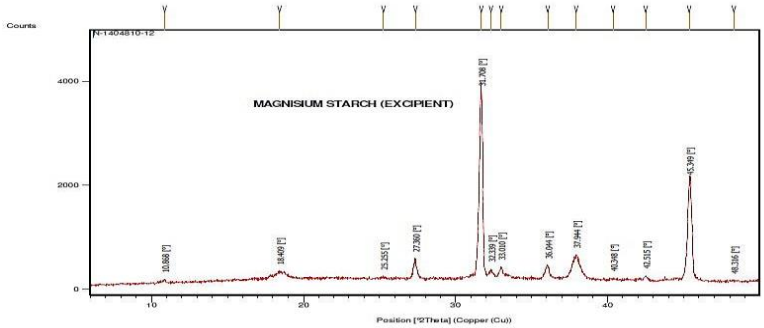

Fig .3: XRD of Magnesium Starch

Table 4: Physical and Micromeritic Properties of the Magnesium Starch Prepared

Parameters	Observation
Solubility	Slightly soluble in water
pH (1% w/v aqueous dispersion)	3.52
Melting point	192°C
Viscosity(1%w/v aqueous dispersion)	1.206 cp
Swelling index	60.4
Gelling property	No gelling and the swollen particles of magnesium starch separated from water. Where as in the case of starch, it was gelatinized and formed gel
Moisture absorption	4.5%
Particle size	168 µm (80/120 mesh)
Density	0.9991 gm/c.c
Bulk density	0.557 gm/c.c
Tapered density	0.65 gm/c.c
Angle of repose	26.56
Compressibility index	16.66

The compatibility of magnesium starch with the selected drug (diltiazem hydrochloride) was evaluated by DSC, FTIR and TLC studies. The DSC thermograms of diltiazem hydrochloride (DH) and diltiazem hydrochloride –magnesium starch (DH-MS) are shown in figs 4 and 5. The DSC thermograms of DH and DH-MS exhibited exothermic peaks at 217.14^0 Cand 210.87^0 C respectively. These melting peaks of DH and DH-MS correspond to the melting point of diltiazem hydrochloride (212 - 214^0 C). The melting peaks observed in the DSC thermograms of diltiazem hydrochloride and diltiazem hydrochloride – MS mixtures correspond to the melting points of the respective drug indicating no interactions between the selected drug and Magnesium starch polymer. The DSC study thus indicated no interaction between magnesium starch and selected drug.

The FTIR spectra of DH and DH-MS are shown in figs 6 and 7. The characteristic FTIR bands of diltiazem hydrochloride at 3343.20 cm^{-1} (N – H), 2837.97cm^{-1}(C – H) were all observed in the FTIR spectra of both DH and DH-MS. These FTIR spectral observations also indicated no interaction between magnesium starch and the drug selected.

In the TLC study, single spots were observed in the case of pure drugs as well as their mixtures with magnesium starch the close agreement of the R_f values of the drugs and their mixtures with magnesium starch (table 5) indicated no interaction between the drug and magnesium starch.

The compatibility of magnesium starch with the selected drug (diltiazem hydrochloride) was evaluated by DSC, FTIR and TLC studies. The DSC thermograms of diltiazem hydrochloride (DH) and diltiazem hydrochloride –magnesium starch (DH-MS) are shown in figs 5.3 and 5.4. The DSC thermograms of DH and DH-MS exhibited exothermic peaks at 217.14^0 Cand 210.87^0 C respectively. These melting peaks of DH and DH-MS correspond to the melting point of diltiazem hydrochloride (212 - 214^0 C). The melting peaks observed in the DSC thermograms of diltiazem hydrochloride and diltiazem hydrochloride – MS mixtures correspond to the melting points of the respective drug indicating no interactions between the selected drug and Magnesium starch polymer. The DSC study thus indicated no interaction between magnesium starch and selected drug.

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Thus, the results of DSC, FTIR and TLC indicated no interaction between the selected drug and magnesium starch, the chronotherapeutic polymer. Hence, magnesium starch could be used as a polymer in the design of chronotherapeutic drug delivery of selected drug.

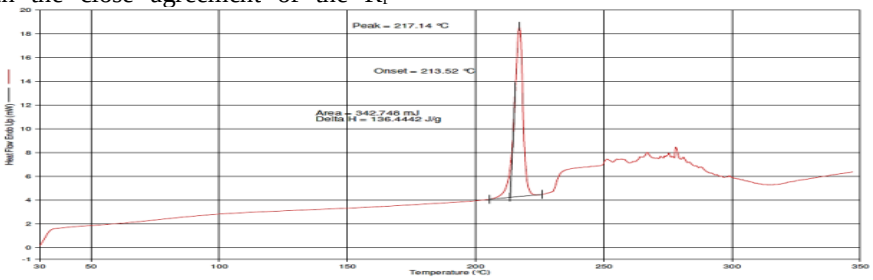

Fig 4: DSC Thermogram of Diltiazem Hydrochloride Pure Drug

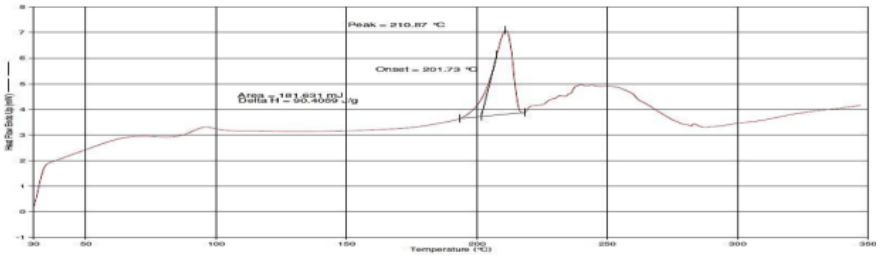

Fig 5: DSC Thermogram of Diltiazem Hydrochloride with Magnesium Starch

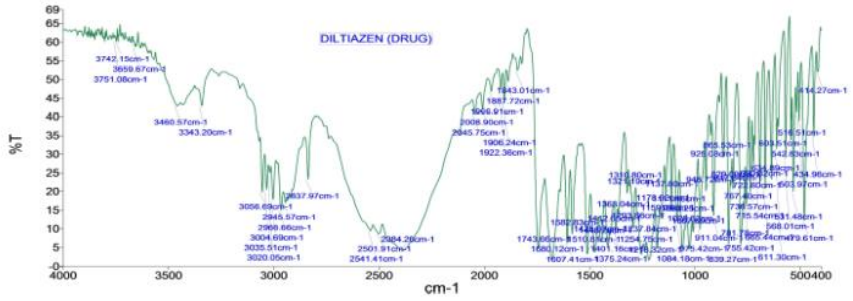

Fig 6: FTIR Spectra of Diltiazem Hydrochloride Pure Drug

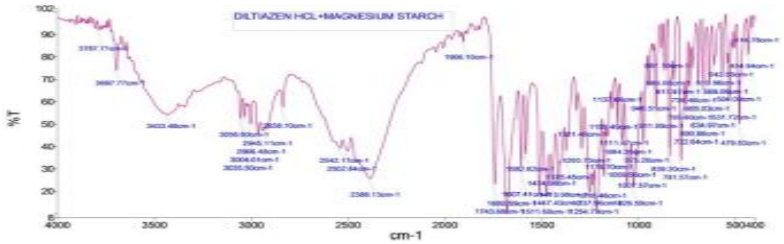

Fig 7: FTIR Spectra of Diltiazem Hydrochloride and Magnesium Starch

Table 5: R_f Values of Selected Drugs and their Mixtures (1:1) with Magnesium Starch

S.No	Product	R_f Value
1.	Diltiazem hydrochloride	0.754 ± 0.002
2.	Diltiazem hydrochloride – Magnesium starch	0.714 ± 0.003

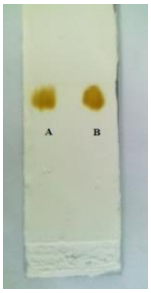

Fig.8: TLC Plate Showing (A) Diltiazem Hydrochloride Pure Drug (B) Diltiazem Hydrochloride and Magnesium Starch

Pre compression and coated material powder blend were evaluated for angle of repose, bulk density, tapered density and compressibility index. The values for angle of repose and compressibility index were found to be good correlation indicating that all formulations possess good flow property and compressibility (shown in Table 6, 7, 8)

Table 6. Pre compression of Core Tablets Material Powder Blend

Formulation	Bulk Density gm/cm^3	Tapered Density	Compressibility Index	Angle of Repose
F1	0.512±0.015	0.582±0.001	21.59±2.43	25.98±0.89
F2	0.445±0.081	0.549±0.017	18.55±3.90	26.92±1.31
F3	0.421±0.016	0.538±0.025	17.53±2.44	23.88±0.31
F4	0.342±0.017	0.425±0.020	22.73±0.89	22.98±0.44
F5	0.495±0.018	0.624±0.011	18.90±1.36	24.53±0.56

Table 7: Pre compression Parameters of Coated Material Powder Blend Employing Eudragit-L 100 as Chronotherapeutic Polymer

Formulation	Bulk Density gm/cm^3	Tapered Density	Compressibility Index	Angle of Repose
DE1	0.521±0.018	0.771 ± 0.015	19.70 ± 3.42	21.47 ± 1.23
DE2	0.518±0.014	0.621 ± 0.019	17.52 ± 2.16	31.67 ± 1.17
DE3	0.470 ± 0.007	0.537 ± 0.008	11.14 ± 2.31	31.31 ± 0.30
DE4	0.443 ± 0.021	0.489 ± 0.014	7.843 ± 2.42	24.53 ± 0.20
DE5	0.369 ± 0.004	0.439 ± 0.015	15.97 ± 1.62	20.21 ± 0.77

Table 8: Pre compression Parameters of Coated Material Powder Blend Employing Magnesium Starch as Chronotherapeutic Polymer

Formulation	Bulk Density gm/cm^3	Tapered density	Compressibility index	Angle of Repose
DM1	0.532 ± 0.008	0.773 ± 0.011	18.70 ± 2.42	20.37 ± 1.23
DM2	0.521 ± 0.013	0.630 ± 019	18.12 ± 2.16	32.33 ± 1.03
DM3	0.475 ± 0.011	0.543 ± 0.008	13.31 ± 1.32	30.25 ± 0.21
DM4	0.454 ± 0.021	0.491 ± 0.006	8.43 ± 2.42	21.13 ± 0.32
DM5	0.373 ± 0.032	0.444 ± 0.021	14.63 ± 1.62	20.22 ± 0.16

The core tablets are subjected to weight variation, hardness, friability and percent drug contents. Weight variation and hardness are found to be within acceptable limits. The friability was below 1% for all the formulation, which is an indication of good mechanical resistance of the tablet. Drug content of core tablets were observed within the range of 55 – 99.0%. The press coated tablets were subjected for weight variation, diameter, hardness and friability. Weight variation and hardness were found to be within acceptable limit (shown in table 9, 10, 11)

Table 9: Characteristics of Core Tablets

Formulation	Weight Variation (mg)	Hardness (kg/cm^2)	Friability (Percent loss of Weight)	Percent Drug Content
F1	99.50 ± 0.36	3.12 ± 0.12	0.30 ± 0.012	98.50 ± 0.68
F2	99.58 ± 0.35	3.45 ± 0.14	0.31 ± 0.015	98.25 ± 0.72
F3	99.45 ± 0.31	3.39 ± 0.17	0.38 ± 0.015	95.33 ± 0.11
F4	99.60 ± 0.32	3.56 ± 0.11	0.42 ± 0.014	99.02 ± 0.30
F5	99.75 ± 0.39	3.64 ± 0.13	0.21 ± 0.013	99.22 ± 0.30

Table 10: Characteristics of Press Coated Tablets

Formulation	Weight Variation (mg)	Hardness (kg/cm^2)	Friability (Percent loss of Weight)
DE1	194.50 ± 3.40	6.33 ± 0.12	0.05 ± 0.013
DE2	195.70 ± 3.32	6.23 ± 0.14	0.15 ± 0.014
DE3	198.50 ± 2.54	6.49 ± 0.11	0.22 ± 0.015
DE4	198.81 ± 2.91	6.54 ± 0.15	0.32 ± 0.014
DE5	198.89 ± 2.07	6.46 ± 0.13	0.35 ± 0.015

Table 11: Characteristics of Press Coated Tablets

Formulation	Weight Variation (mg)	Hardness (kg/cm^2)	Friability (Percent loss of Weight)
DE1	194.50 ± 3.40	6.33 ± 0.12	0.05 ± 0.013
DE2	195.70 ± 3.32	6.23 ± 0.14	0.15 ± 0.014
DE3	198.50 ± 2.54	6.49 ± 0.11	0.22 ± 0.015
DE4	198.81 ± 2.91	6.54 ± 0.15	0.32 ± 0.014
DE5	198.89 ± 2.07	6.46 ± 0.13	0.35 ± 0.015

***In-vitro* Dissolution of Core Tablets**

The effects of Crospovidone level on drug release profile from uncoated tablet (Formulations F1 to F5) were determined. As amount of Crospovidone increases from formulations F1 to F5; the following containing highest amount (10%) of Crospovidone (F5) showed fast disintegration.

***In-vitro* Dissolution of Press Coated Tablets**

Formulations DE1 to DE5 (fig 10) showed increase in lag time and decrease in diltiazem hydrochloride release rate with increase on weight ratio of HPMC K-15M. When Eudragit L-100 combines with HPMC K-15M, the viscosity of the mixture increases as the ratio is increased. Upon contact with the dissolution medium, it formed a gel like structure. But due to presence of Eudragit L-100 in greater amount in DE1 the gel formed is capable enough to hold the drug for long time, instead started to erode and allow dissolution medium to penetrate into the core tablet and there was bursting effect. In case of DE2, the lag time was 9 hours, after 9 hours there was a sudden release of large quantity of drug, which can show therapeutic effect at the time the blood pressure in patient will be increased. In case of DE3, DE4 and DE5, the lag time was more than 10 hours, and they are not appropriate for chronotherapeutic drug delivery. Therefore Eudragit L-100: HPMC K-15M in the ration of 75:25 is ideal for chronotherapeutic delivery with appropriate lag time and almost complete release rate.

Here the prepared Magnesium starch was used in the place of Eudragit L-100 and the ration with HPMC K-15M is repeated and their dissolution was observed. It was observed that formulation DM1 to DM5 showed increase in lag time and decrease in diltiazem hydrochloride release rate with increase on weight ratio of HPMC K-15M. When Magnesium starch combines with HPMC K-15M, the viscosity of the mixture increases as the ratio is increased. Similar to that of Eudragit L-100 the Magnesium starch showed formation of gel like structure and in formulation DM2, the lag time was observed as 9 hours, after 9 hours there was a sudden release of large quantity of drug, which can show therapeutic effect at the time the blood pressure in patient will be increased. Here the amount of drug dissolved is more when compared to that of formulation using Eudragit L-100 (fig 11). In case of DM3, DM4 and DM5, the lag time was more than 10 hours, and they are not appropriate for chronotherapeutic drug delivery. Therefore Magnesium starch: HPMC K-15M in the ration of 75:25 is ideal for chronotherapeutic delivery with appropriate lag time and complete release rate when compared to that of Eudragit L-100: HPMC K-15M in the ration of 75:25.

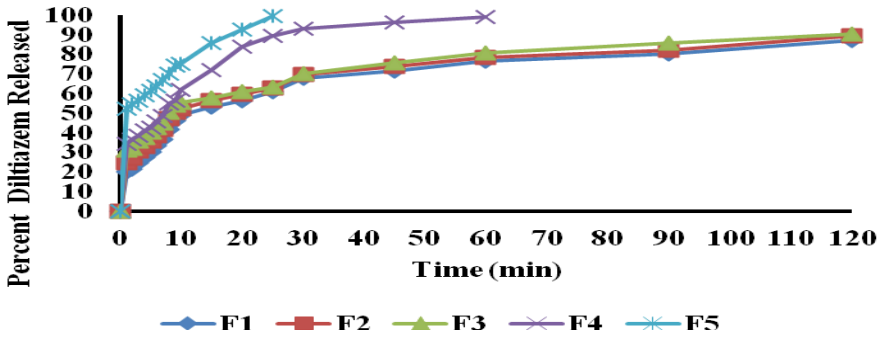

Fig 9: Dissolution Profiles of Core Tablets (F1 – F5)

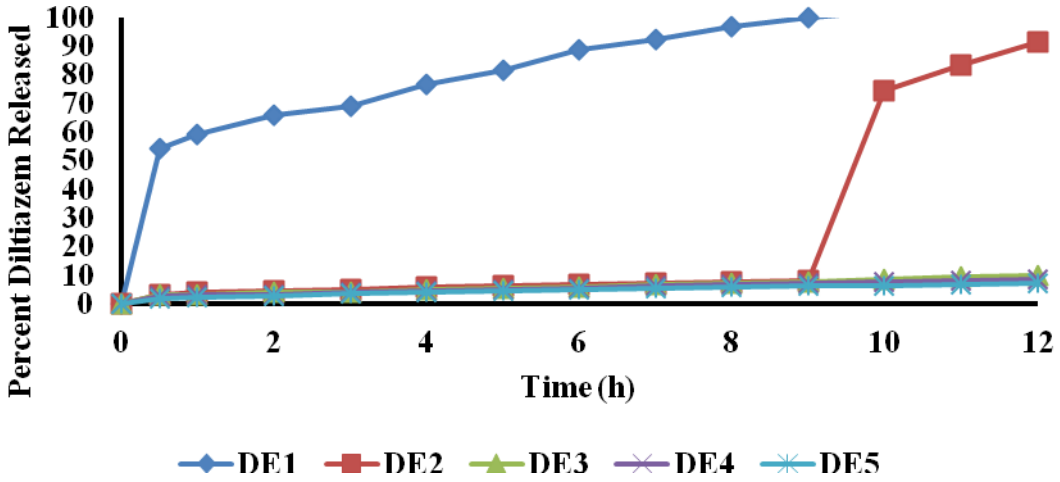

Fig 10: Release Profiles of Press Coated Tablets (DE1 – DE5)

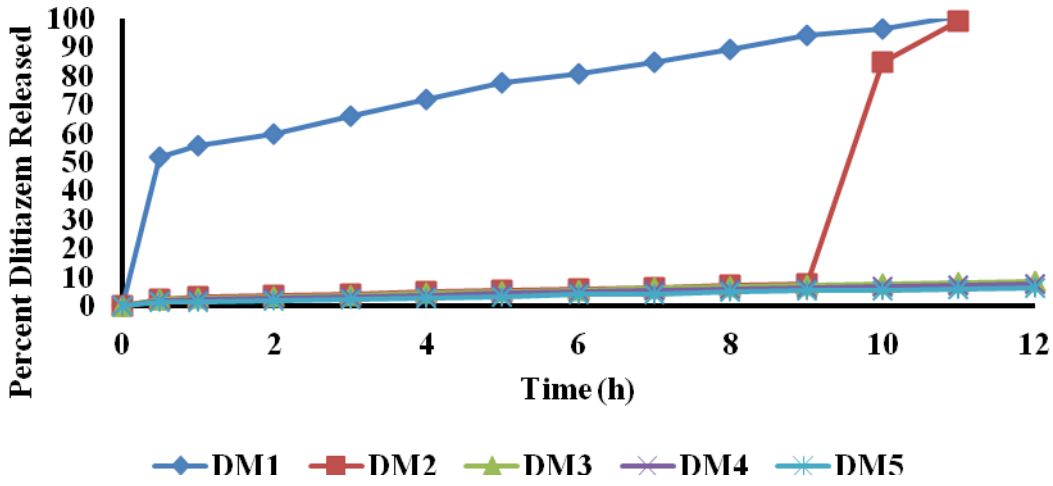

Fig 11: Release Profiles of Press Coated Tablets (DM1 – DM5)

Pre compression and coated material powder blend were evaluated for angle of repose, bulk density, tapered density and compressibility index. The values for angle of repose and compressibility index were found to be good correlation indicating that all formulations possess good flow property and compressibility (shown in Table 6, 7, 8).

CONCLUSION:

Press coated tablets of diltiazem hydrochloride utilizing Magnesium starch: HPMC K-15 in the ratio of 75:25 displayed timed release dissolution i.e., a lag phase was observed in the dissolution profile and the drug was rapidly after complete erosion of the outer coating. All the core and press coated tablets of diltiazem hydrochloride employing Magnesium starch as chronotherapeutic polymer and other known polymer were are of good quality with regard to drug content, hardness and friability and fulfilled the official (IP/USP) requirements with regard to the above mentioned physical properties. Formulations DE1 TO DE5 showed increase in lag time and decrease in diltiazem hydrochloride release rate with increase in weight ratio of HPMC K-15M. When Eudragit L-100 combines with HPMC K-15M, the viscosity of this mixture increases as the ratio increased Eudragit L-100:HPMC K-15 M when used the ratio of 75:25 showed an appropriate lag time of 9 hours and almost complete release of drug (91.28%) within 10 hours. The same F5 formulated tablets

were coated by using Magnesium starch instead of Eudragit L-100. Formulations DM1 to DM5 are prepared using various ratios of Magnesium starch: HPMC K-15 M. They showed an increase in lag time and decrease in diltiazem hydrochloride release rate with increase in HPMC K-15 M. When Magnesium starch is combined with HPMC K-15 M, viscosity of the mixture increases as the ratio increased. Magnesium starch: HPMC K-15 M in the ratio of 75:25 is ideal for chronotherapeutic drug delivery which showed an appropriate lag time of 9 hours and completes release of drug (99.20%) within 10 hours.Formulations containing Magnesium starch showed better lag time for about 9 hours and release the drug completely in 10 hours.**Thus, the polymer Magnesium starch could be used in the formulation of chronotherapeutic drug delivery systems.**

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