Formulation And Evaluation of Bilayers Tablets of Montelukast Sodium Immediate Release and Bilastine Sustained Release`

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Abstract

The objective of present work is to formulation and evaluation of bilayers Tablets of montelukast sodium immediate release and bilastine sustained release for treating allergic rhinitis effectively. The combining Montelukast with bilastine gives additional benefits. The tablet formulating Montelukast in immediate release layer and bilastine as sustained release layer as it improves and increases the stability by reducing the acid base interactions of both the drugs in combination, increasing the bioavailability. In this research many polymers used but natural polymer pectin is used as a release retardant for sustained release layer. The formulations were evaluated for hardness, weight variation, friability, and drug content uniformity. The in vitro release of drug from the formulations was studied in pH 1.2 acidic buffers and pH 7.4 phosphate buffer, and it was found that the prepared tablets were able to sustain the release of the drug upto 12hours. The release of Montelukast and bilastine of both layers from the tablets was found to be diffusion controlled and the release mechanism was non-Fickian based on the n value of Korsmeyer-peppas plot. The FTIR studies were performed on three optimized formulations (F5) and the plain drug controls(Bilastine ,Montelukast). From the observed peaks it is evident that the polymers used and the drugs were found to be mutually compatible chemically. The dissolution results indicate that the formulation optimised with pectin was able to sustain the release of bilastine upto 12hours. So that the studies indicating efficient sustained action and improved bioavailability of the drug. The formulated bilayered tablets using natural polymers provided immediate release of montelukast and sustained release of bilastine and therefore hold promise as an alternative dosage form in the treatment of allergic rhinitis, urticaria and bronchial asthma.

Key Words: Allergic Rhinitis, Urticaria, Montelukast sodium, Bilastine

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Introduction

Oral ingestion has long been the most convenient and commonly employed route of drug delivery due to its ease of administration. It is well known that modified release dosage forms may offer one or more advantages over immediate release formulations of the same drug. There are many ways to design modified release dosage forms for oral administration; from film coated pellets, tablets or capsules to more sophisticated and complicated delivery systems such as osmotically driven systems, systems controlled by ion exchange mechanism, systems using three dimensional printing technology and systems using electrostatic deposition technology [1].

Applications [2]

Bi-layer tablet is suitable for sequential release of two drugs in combination.

Separate two Incompatible substances, Sustained release tablet in which one Layer is immediate release as initial dose and second layer is maintenance dose.

Promoting patient Convenience and Compliance.

Disadvantages of bilayer Tablet

Bitter tasting drugs, drugs with an objectionable odour or drugs that are sensitive to oxygen may require encapsulation or coating.

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Difficult to swallow in case of children and unconscious patients.

Ideal Characteristics of bilayer Tablets

A bi-layer tablet should have elegant product identity while free of defects like chips, cracks, discoloration and contamination.
It should have sufficient strength to with stand mechanical shock during its production packaging, shipping and dispensing.

Material And Method

Bilastine was a kind gift from Symed labs, Hyderabad, India, Montelukast sodium was a kind gift sample from Matrix laboratories, Hyderabad, India. Hydroxy propyl methyl cellulose was purchased from Colocron Asia Pvt limited India. Poly Vinyl Pyrollidine (PVP) K90D was a kind gift sample from Dr. Reddy's Laboratories,Hyderabad. All the solvents used were of HPLC grade purchased from Merck Chemicals,India.

Methods

Isolation Pectin

Pectin extraction was performed using various conditions such as (6M HCl, 1N H_2SO_4, 1N HNO_3, 6.2g/100g citric acid, 1N acetic acid, combination with acetic acid and ammonium oxalate and distilled water), extraction temperature (70, 80, 90 and 1000 °C) and extraction time (30, 60, 90 and 120 min). The pH for all acids solutions was maintained at 2 while the pH of the acetic acid and ammonium oxalate combined acid solution was set at 4.6. The pH of water was almost 7.0. For each condition, 30 parts extraction solvent with 1 part lemon pomace powder was heated in hot water bath. After heating the extractant was filtered with cheese cloth and pressed the extract. The pectin was precipitated by adding absolute ethanol (95-98%) in the ratio of 1 part extractant to 2 parts ethanol and kept at room temperature for overnight. The precipitated pectin was filtered through the filter paper whatman No. 4 and washed with 75% ethanol (v/v), 85% ethanol (v/v) and absolute ethanol to remove the soluble impurities. The pectin was dried at 400C for 24 hours in a cabinet drier . Optimum conditions such as distilled water solution, extraction time 1h, and extraction temperature 1000°C were selected based on pectin yield and Equivalent weight [3]

Preformulation studies

Standardization of drug

UV Spectrophotometric method
The drug was analyzed by using LAB INDIA UV-1800 spectrophotometer having double beam detector configuration. Standard curve was plotted in 0.1N HCL at the maximum wavelength of 273nm [70].

Fourier transformation infra –red analysis

Drug- excipients compatibility studies the infra red absorption spectra of unmixed drug & with unalike ingredient were hold in the scale of four hundred thousand to four hundred cm-1 using KBr dise procedure, 1-2 milligram of material to be analyse was mixed with 300-400 mg, specified quantity of minute powder & dried KBr these sum are mainly enough to give a circle of 10-15 diameter and pellet of right strength by a hydraulic press [4].

Micrometry

Angle of repose of powder

Mostly funnel is used in this method, firstly weight of the powder and it taken in a funnel, the height (h) funnel is place in a stand, after the powder is place in the funnel to freely flow, then the angle of repose of the powder is find out. Range of repose can zero degree. The angle of repose of the powder is found out the following formula [5].

$$\tan \theta = h/r \quad (1)$$

..... (1.1)

Therefore, $\theta = \tan h/r$

Here, θ = angle of repose
h = height of the pile
r = radius of the pile base

Bulk density

Bulk density is calculated by adding a known mass powder to a cylinder. The density is calculated as mass.
Tapped density in this method firstly we have to weigh the known powder and then the known powder transfer in a 10 ml mechanically tapping cylinder. The tapping is started until the little further volume changed is observed [6].
Calculated by following equation
Loosen bulk density = total mass of powder /volume of powder
Tapped bulk density = powder wt. / tapped volume

Carr's index

Carr's index help in measuring the power need to breakdown the friction into the particle & the hopper. Carr's index > 25 % is carefully to be a sign of low flow capability, and under 15, of good flow property It can be calculated by following equation [7, 8].

Carr's index (%) = [(total bulk density –loosen bulk density) ×100]/TBD

Where TBD = tapped bulk density

Hausner ratio: Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula. Hausner's Ratio = Tapped density / Bulk Density

Preparation of Bilayer Tablets

Immediate release (Montelukast Sodium)

Montelukast tablets were prepared by wet granulation method. Montelukast, super disintegrants (Sodium starch glycolate, croscarmellose) and lactose were weighed as in Table1 and mixed thoroughly. Starch Paste (5%) was used as a Binder. The wet mass was passed through sieve no 12. The obtained granules were dried at 40°C for 30min in tray drier. The dried granules were screened through sieve no 22 and later using sieve no.44 Magnesium stearate(1%) and talc(q.s) were used for lubrication.

Sustained release layer: (Bilastine)

Bilastine sodium tablets were also prepared by wet granulation method. Specified quantity of drug, polymer Pectin, HPMC Grades K100M, K15M.) And microcrystalline cellulose were weighed as in Table 2 and mixed thoroughly. PVP (1%) was used as binder. Granules were obtained by passing the sluggy mass through sieve no 12. The prepared granules were dried at 40°C in a tray drier for 1 hour. The dried granules were screened through sieve no 22. Magnesium stearate (1%) and Talc (q.s) were finally added and mixed by triangular mixing. These lubricated granules were compressed into tablets weighing about 250 mg containing 75 mg of Montelukast and 175mg Bilastine in a Rotary tablet compression machine (12 station, RIMEK, India) using 9 mm circular, flat punches plain on both sides .The compressed tablets

Were stored in HDPE containers for stability studies

Evaluation Parameters of all formulations

Tablet hardness

Tablet hardness is laboratory techniques in this technique we have check the hardness of tablets in case of storage and handling before usage. The hardness of the tablets we can perform by using the hardness tester like Monsanto hardness tester, 6 tablets each batch crushing with known weight was recorded in kg/cm2 and average weight was calculated [9].

Friability of tablets

Friability is defined as it is capacity of a solid material break into smaller pieces in case of transportation. Friability follows the following procedure. Firstly 20 tablet taken and weight accurately and place in a plastic chamber and set the chamber at 25 rpm for 4 minutes, after the 4 min and 100 revolutions stop the Roche apparatus and reweight the 20 tablets and Calculate the loss in tablet weight by the following formula [10].

%weight loss = initial of tablet – final weights of tablets/ final weights ×100 ..... (4.3)

Weight variation

Weight variation is define as to ensure that each of tablet carry proper amount of drug. This method is performed as, weight of 20 individual tablet using analytical balance, after that calculate the average weight of tablet, and after that calculate the individual tablet weight to the average [11].

% of weight Variation = average wt–average wt individual wt / average wt× 100..... (4.4)

Drug content of Montelukast layer: [11]

Ten tablets of each formulation were weighed and powdered. A quantity of powder equivalent to 10 mg of Montelukast was taken into 50 ml volumetric flask. The amount of drug present in a 10 mg equivalent amount of powder was dissolved in 0.5% SLS solution. The volume of this solution (2ml) was taken and diluted with water up to 10ml with methanol . UV absorbance was Measured at 344 nm.

In vitro drug release studies [12]

The release of drug from different batches of prepared tablets was studied by using USP paddle type II dissolution apparatus [11]. Buffer was used as dissolution medium pH 1.2 for 2 h and phosphate buffer of pH 7.4for 12 h. The medium volume was maintained at 900ml, the temperature was maintained at 37°C ± 0.5°C and the stirring rate was 50 RPM. Samples were withdrawn at regular time intervals and the same volume was replaced with fresh dissolution medium. The samples were measured by UV Spectrophotometer at 231 nm for immediate release layer Bilastine and Montelukast

at 344nm for sustained release layer against a blank.

Stability Studies [13]

Stability studies are a most important part of the improving of the life of pharmaceutical dosage form. They allow the evaluation of API Drug product stability studies is finding out of the main acceptable preparation as per international conference of Harmonisation guideline at 40±2°C/ 75± 5%. There is a no major change in the physical and chemical properties of tablet of formulation F5 after 3 months.

Result And Discussion

UV Spectroscopy-

After scanning of the sample drug, the wavelength was obtained about 310 nm in pH 7.4 phosphate buffers by using UV Spectroscopy Method.

Table 3.1 Calibration Curve of Montelukast and Bilastine

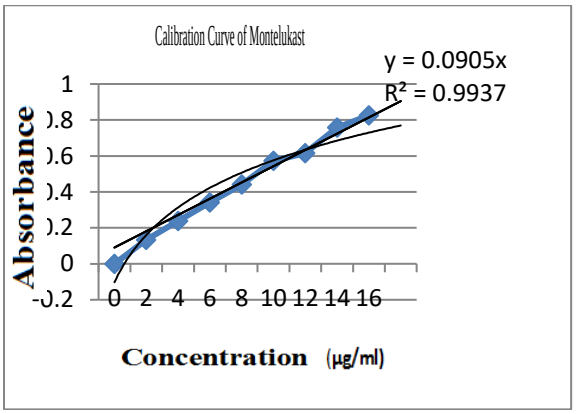


Fig 1 Calibration Curve of Montelukast

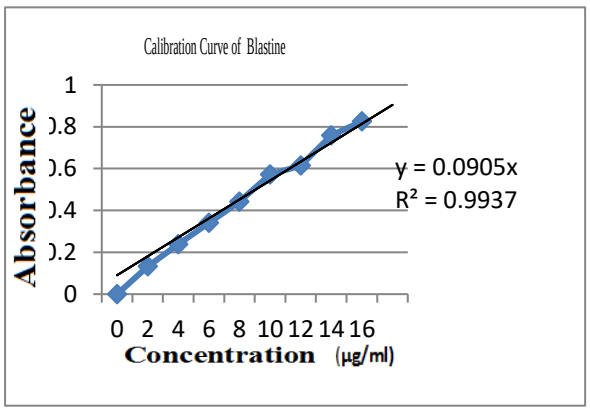
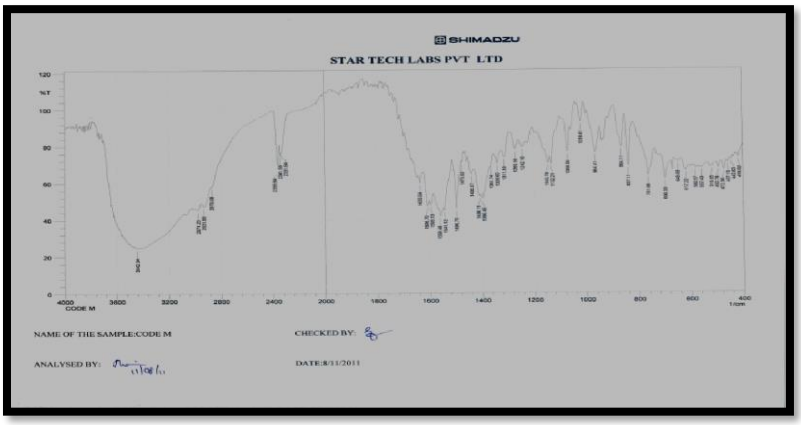


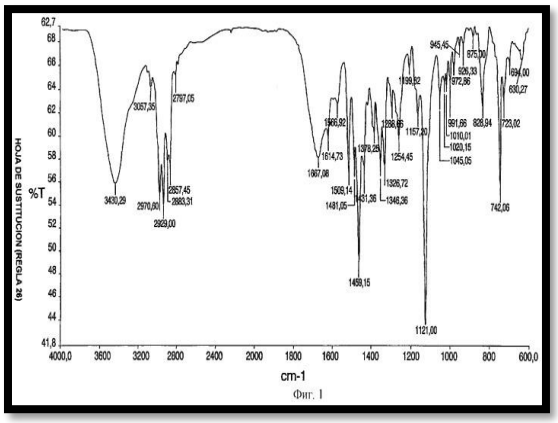
Fig 3.2 Calibration Curve of Bilastine

Fourier transform infrared

The FTIR studies of pure drugs Blasting and montelukast ,the natural polymer Pectin and optimized formulations (F5) were carried out to detect any major interfering incompatibility between the drugs and the polymer .



FTIR 3 spectrum of pure drug montelukast



FTIR 4 spectrum of pure drug Bilastine

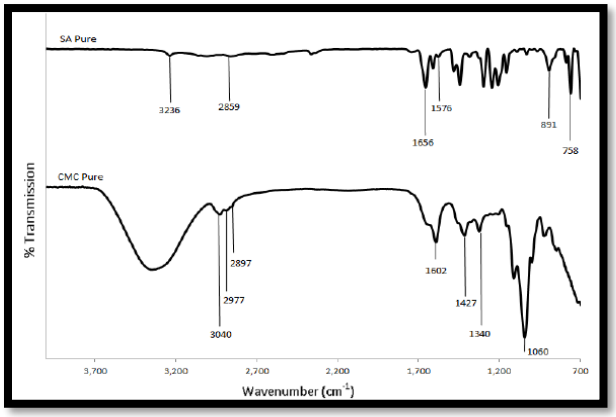


Fig 5 FTIR Montelukast+ CMC

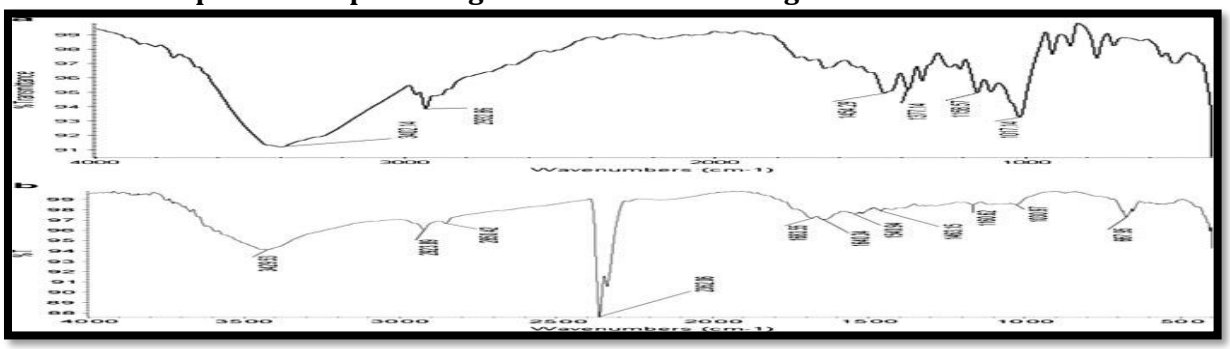


Fig 6 FTIR of Bilastine with Pectin

Evaluation of immediate release Montelukast Granules

Table 2: Evaluation parameter of Montelukast

F CODE	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's Index	Hausner's ratio	Angle of repose (°)
F1	0.434 ± 0.04	0.481 ± 0.03	10.25 ± 0.12	1.13 ± 0.03	28.90 ± 0.16
F2	0.425± 0.04	0.478 ± 0.04	10.83 ± 0.11	1.11 ± 0.03	29.25 ± 0.16
F3	0.442 ± 0.03	0.479 ± 0.04	12.21 ± 0.13	1.12 ± 0.03	27.12 ± 0.16
F4	0.447 ± 0.05	0.470 ± 0.03	10.10 ± 0.12	1.13 ± 0.03	30.32 ± 0.16
F5	0.422 ± 0.04	0.460 ± 0.05	9.14 ± 0.13	1.9 ± 0.03	26.23 ± 0.16

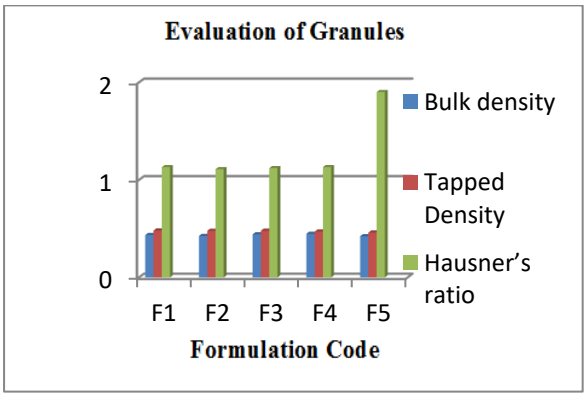


Fig 7 Evaluation of Granules of - immediate release Montelukast,

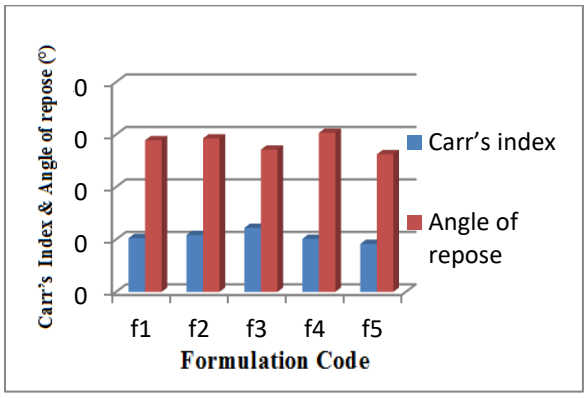


Fig 8 Carr's index and Angle of repose of immediate release Montelukast

Table 3: Precompressional parameter of Bilastine

F CODE	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's Index	Hausner's ratio	Angle of repose (°)
F1	0.439 ± 0.02	0.501± 0.01	12.00 ± 0.13	1.11 ± 0.04	32.14 ± 0.11
F2	0.441 ± 0.03	0.412 ± 0.04	11.00 ± 0.10	1.12 ± 0.03	30.85 ± 0.12
F3	0.440 ± 0.02	0.489 ± 0.02	13.00 ± 0.11	1.10 ± 0.03	29.85 ± 0.10
F4	0.442 ± 0.03	0.512 ± 0.2	10.14 ± 0.10	1.12 ± 0.04	28.02 ± 0.11
F5	0.441 ± 0.01	0.479 ± 0.03	8.90 ± 0.12	1.9 ± 0.04	26.85 ± 0.15

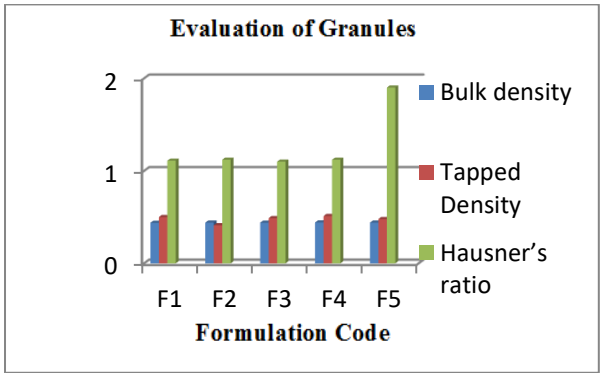


Fig 9 Bulk, Tapped density and Hausner's Ratio of sustained release Bilastine Granules

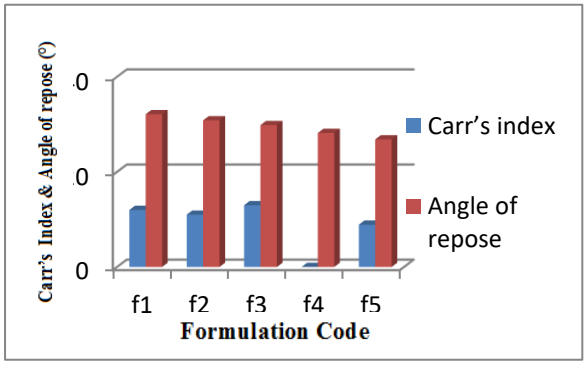


Fig 10 Carr's index and Angle of sustained release Bilastine Granules

Post compression evaluation Parameter of Immediate release Montelukast Sodium

Tablet: 4 evaluation parameter of montelukast sodium

F Code	Hardness(kg/cm2)*	Friability (%)*	% Weight variation	% Drug content
F1	4.2 ± 0.25	0.018 ± 0.03	1.2 ± 0.01	73.84 ± 2.14
F2	3.1±0.23	0.012±0.02	1.3±0.03	78.14±2.21
F3	4.5±0.18	0.012±0.01	0.785±0.02	87±1.25
F4	3.6±0.26	0.05±0.03	0.68±0.04	91.7±1.58
F5	3.0±0.12	0.004±0.02	0.08±0.01	96.80±2.69

Post compression evaluation Parameter of Sustained release Bilastine

Tablet 5: Post compression evaluation Parameter of Sustained release Bilastine

F Code	Hardness(kg/cm2)*	Friability (%)**	% Weight variation	% Drug content
F1	4.1 ± 0.25	0.018 ± 0.03	1.9 ± 0.01	71.84 ± 2.14
F2	3.7±0.13	0.072±0.02	1.3±0.03	78.14±1.21
F3	4.5±0.18	0.012±0.01	0.78±0.02	89±1.24
F4	6.6±0.26	0.09±0.03	0.68±0.04	90.7±1.58
F5	3.0±0.12	0.003±0.02	0.09±0.01	95.74±1.61

In vitro drug release studies

Cumulative % Drug release of immediate release montelukast layer

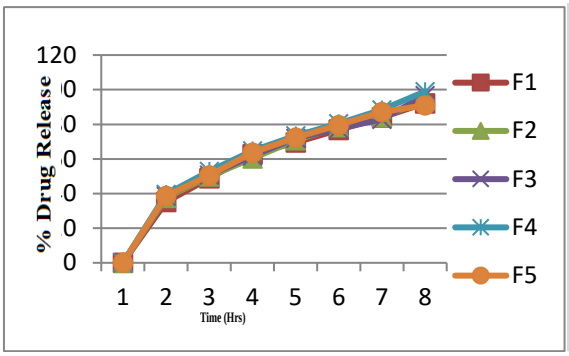


Fig 15: Drug release of immediate montelukast

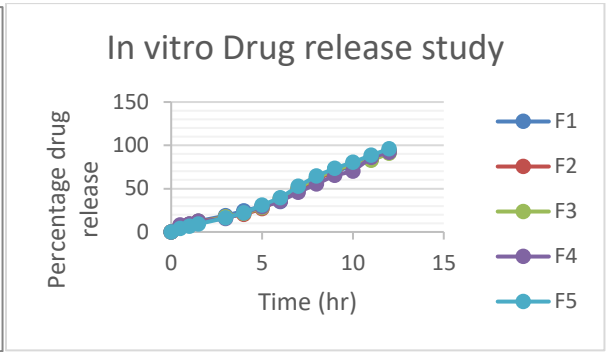


Fig 16: Drug release from Sustained release release bilastine layer

Stability Studies

We have take sample of both immediate release and sustained release of best formulation F5 The duration of stability studies, there is no major variation in, the minor variation found in hardness, Disintegration time and In vitro drug release that is adjustable, All data evaluated according to ICH guidelines at 40±2°C/75±5% RH for 90 days.

Conclusion

The prepared bilayered tablets of Montelukast and bilastine using sodium starch glycolate and Croscarmellose sodium showed immediate release of montelukast layer in 30 min (F5). The second layer formulated using pectin (F 5) showed sustained release up to 12 hours compared to the formulations (F4, F3, F2) using HPMC Grades (K100M, K15M, K4M). From the stability studies Bilayered tablets with natural polymer pectin were found to be stable. The formulated Sustained release bilayered tablets (F5) showed significantly higher Cmax compared to control formulations. Hence from our investigations we can conclude that the bilayered tablets of motelukast and bilastine prepared using natural polymer pectin are a promising alternative in the effective treatment of patients suffering from Allergic rhinitis, urticaria and bronchial asthma.

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