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COMPRESSED MATRIX CORE TABLETS OF KETOROLAC TROMETHAMINE FOR A QUICK/SLOW DUAL-COMPONENT DRUG DELIVARY

[1]APPA RAO POTU[1], [2]VEERAREDDY PRABHAKAR REDDY
*Balaji Institute of Pharmacy, Laknepally(V), Narsampet (M), Warangal T.S
[2]College of Pharmacy, Palamuru University, Mehabub Nagar-A.P
***Corresponding author:E.Mail:arrpotu@gmail.com**

ABSTRACT

The aim of the present investigation was to design and evaluate compressed matrix core tablets for a biphasic drug delivery of Ketorolac tromethamine as a model drug. A dual component tablet made of a sustained release tablet core and an immediate release tablet coat was prepared by direct compression using various controlled release polymers of differing solubility characteristics such as ethyl cellulose, hydroxy propyl methyl cellulose K100 M and eudragit L100 -55 and super disintegrating agents cross carmellose, cross povidone, and sodium starch glycollate. Both the core and the coat contained fraction of the total dose. Drug fraction contained in the fast releasing component was dissolved within 5-6 minutes depending upon the nature and type of super disintegrating agent, whereas the drug contained in the core tablet was released in a sustained manner for extended periods of time based on the solubility characteristics, drug release mechanisms (≈12 or 18 hours), and on the composition of the matrix tablets. Based on the in vitro drug release profiles and release kinetic parameters calculated, it can be concluded that the compressed core matrices provided the conceived quick/slow biphasic drug delivery. Core matrices released the drug by coupled diffusion and erosion mechanisms.

KEYWORDS: Ketorolac tromethamine, biphasic drug delivery, compressed matrix core, FTIR.

INTRODUCTION

Drug delivery by oral route is the most desirable one for achieving systemic drug effects (Stoner, 2004). Conventional dosage forms of drugs having a short biological half life needs frequent daily administration and produce wide fluctuations in peak and trough steady-state drug levels with a controlled release (CR) formulation, a predictable and reproducible release rates can be achieved with many advantages (Theeuwes, 1983; Hirtz, 1985). The use of controlled-release technology in the design of pharmaceutical dosage forms has become increasingly important in the past few decades (Efentakis, 2000).

The most commonly used method of modulating the drug release is to include it in a matrix system (Salsa, 1997). Matrices are monolithic systems constituted of drug dispersed and entrapped throughout an excipient (adjuvant), i. e., the matrix forming substance (Alderman, 1984). Hydrophilic polymer matrix systems are widely used in oral controlled drug delivery because of their flexibility to obtain a desirable drug release profile, cost-effectiveness, and broad regulatory acceptance (Lapidus, 1968). Hydrophobic and /or Water-insoluble inert carriers have also been used for preparing sustained release dosage forms of various water-soluble and short-acting drugs (Sanchez, 2002).

If, for a certain therapeutic indication, a single rate of drug release is does not totally fulfill the objectives, the biphasic release systems could be utilized (Ammar, 1997). There are many approaches such as bilayer tablets, multi layer tablets compression coated tablets, aqueous coating and compressed mini tablets to achieve biphasic release profile. Maanufacture of layered matrix tablets is associated with some problems such as improper adhering of the layers (Conte, 2000).

Many a times, in drug therapies, rapid availability of drug dose is very much needed in the short time possible in order to relieve the symptoms of the disease, followed by the maintenance of an effective drug plasma level to achieve the desired prolongation of the clinical effects. Suitable candidate drugs, for this type of administration include therapeutic categories such as NSAIDs, anti-hypertensives, anti-histamines, and anti-allergic agents (Uekama, 1990). A quick/slow release system provides an initial burst of drug release followed by a constant rate (ideally) of release over a defined period of time. Hydrophilic polymer matrix systems are widely used in oral controlled drug delivery (Conte, 2000).

Hydrophobic and /or Water-insoluble inert carriers have also been used for preparing sustained release dosage forms of various water-soluble and short-acting drugs (Timmins, 1992). Hydroxy Propyl Methyl Cellulose

(HPMC) is the most widely used in the formulation of sustained release dosage forms. In aqueous fluids, it forms a viscous gel layer behaving as a protective barrier to the influx of water as well as efflux of the drug in solution (Gohel, 2010). Ethylcellulose (EC) is a common water-insoluble polymer and extensively used as a rate-controlling membrane in the design of dosage forms. Several reports have mentioned the use of EC as a directly compressible excipient in a controlled-release matrix or in an immediate release tablets (Upadrashta, 1993). Eudragit Ll00-55 is an anionic co-polymer of methacrylic acid and methyl methacrylate. There have been some reports regarding the use of Eudragit L100-55 as a sustained release carrier. Erosion is the main mechanism of release of drug dispersed in the polymer (Mehta, 2001). A compressed core tablet is a tablet within a tablet. The core consists of a sustained release tablet, which is coated by compression over the whole surface with a fast-disintegrating formulation (Mehta, 2006).

Ketorolac tromethamine (KTM) is a potent non-steroidal anti-inflamatory (NSAIDs) drug, widely recommended for short term management of mild to moderate post-operative pain. It is administered orally in multiple divided doses (10 mg four times a day). KTM's plasma elimination half-life of is about 4 to 5 hours and hence, needs to be administered four times in a day leading to possible poor patient compliance and inadequate pain management (Tiwari, 2003). In the present work, an effort was made to develop and evaluate simple and cost effective controlled duel release compressed matrix core tabletsusing drug release retarding polymers and super disintegrating agents.

MATERIALS AND METHODS

Materials: Ketorolac tromethamine was obtained as gift sample from DR Reddy's Laboratories, Hyderabad, India, Hydroxypropyl methylcellulose [HPMC], Ethy cellulose and Eudragit were purchased from SD Fine Chemicals Ltd (Mumbai India.) All other reagents and chemicals used were of analytical grade.

Table.1.Composition of Core tablet

Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Ketorolac tromethamine	25	25	25	25	25	25	25	25	25	25	25	25
HPMC	100	75	50	25	-	-	-	-	-	-	-	-
Microcrystal cellulose	-	25	50	75	-	25	50	75	-	25	50	25
Ethyl cellulose	-	-	-	-	100	75	50	25	-	-	-	-
Eudragit	-	-	-	-	-	-	-	-	100	75	50	25

Note: All the formulations contain 2%talc and 2%magnesium stearate

Table.2.Composition of Coat

Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Ketorolac tromethamine	15	15	15	15	15	15	15	15	15	15	15	15
Cross povidone	5	7	9	11	-	-	-	-	-	-	-	-
Cross carmellose	-	-	-	-	5	7	9	11	-	-	-	-
Sodium starch glycolate	-	-	-	-	-	-	-	-	5	7	9	11
Microcrystalline cellulose	155	153	151	149	155	153	151	149	155	153	151	149

Preparation of Core Tablet (Slow Release Component): Direct compression method was employed in preparing core tablets from binary mixtures of KTM and matrix-polymers, HPMC, EC and Eudragit (**Table.**1). All materials were sieved to prevent changes in tablet properties due to changes in particle size. The tablet weight was kept at 175 and was prepared with flat-tip punches and dies with a 6-mm diameter.

Preparation of Duel Tablet: (Fast Release Component): This component contained KTM (15 mg), microcrystalline cellulose, and super disintegrating agents. Twelve different duel component tablets were prepared (four of each polymer). The formulae were shown in Table.2. A powder bed consisting of half of the fast releasing component was made in the center of the die of the tablet press. On the top of the bed, previously compressed core tablet was placed. Other remaining half of the fast releasing component powder was added to enclose the core tablet and compressed into a duel tablet.

Evaluation of Core Tablets and Compressed Core Tablets: The prepared core tablets and compressed core tablet were tested as per standard procedure for drug content, weight variation (n = 20) thickness (n = 20), hardness (n = 6) and friability. Hardness of the tablets was tested with Monsanto tablet hardness tester; friability test was carried out by Roche friabilator. Thickness was measured by digital Vernier caliper (Mathews, 2000).

Drug Excipient Compatibility study: The drug and optimized formulation were examined by FTIR spectroscopy to find out the stability of the drug with excipients. KBr disk method was used to obtain the spectra with a scanning range of 4000–500 cm–1. (FTIR-8400 S, Brucker, Japan). Spectra was examined for any shifts in the peaks and compared with spectra of pure drug for any possible changes in the peaks

Content uniformity: The drug was extracted from the tablets by using methanol. Twenty tablets were crushed and triturated. Weight equivalent to one average tablet was taken in a separating funnel containing methanol and it was shaken vigorously to extract the drug. It was filtered and from the filtrate suitable aliquots were taken and diluted suitably with methanol. The absorbance was measured at 322 nm. The drug content in the compressed matrices was calculated from the calibration curve of KTM.

***In Vitro* Release testing of the duel tablet:** The in vitro release studies were performed using dissolution apparatus I paddle apparatus (Electro lab, Mumbai, India.) at 50 rpm containing 600 mL of 0.1N HCL at 37-C ± 0.5-C. as the dissolution medium. The drug released was spectrophotometrically quantified through a UV/Visible spectrophotometer at 322 nm. The cumulative fraction of the drug released was calculated from the total amount of KTM and plotted as a function of time. Dissolution studies (n = 3) were performed on both compressed core tablet systems and core tablets (Costa, 2001).

Kinetics of drug release and mechanism: Several equations have been reported in the literature to identify the mechanism of drug release from the compressed matrices. The data was evaluated according to the zero order, Highuchi, and Korsmeyer- Peppas models (Patil, 2010).

Stability Studies: Long term stability studies were conducted on the selected formulation by storing them at ambient temperatures (25 °C) and 40% relative humidity (RH) for twelve months. At each sample time (every 3 months) the formulations were assessed for any changes in mechanical properties and drug release profile (Brabander, 2000).

RESULTS AND DISCUSSION

Physical properties: Results of physical evaluation tests of prepared core and duel tablets are depicted in tables 3 and 4 respectively. As is seen from the data, tablets were produced with small weight variations and uniform thickness. Higher friability values were found in case of duel tablets compared to the core tablets. This could be attributed to the moderate adhesion of the coatings to the compressed cores (Waterman, 2003).

Table.3.Physical evaluation of Core tablets

Formulation	Weight variation*(mg)	Hardness** (kg/cm^2) ± Avg S.D (0.327)	Friability (%)	Drug content uniformity*** (%)
F1	120±0.24	4.20	0.32	96.14±0.63
F2	116±0.35	4.57	0.37	95.54±1.05
F3	119±1.98	4.83	0.32	98.18±0.81
F4	117±0.65	4.65	0.38	94.72±1.35
F5	123±2.24	4.91	0.29	93.03±0.66
F6	127±4.5	4.89	0.42	94.82±0.81
F7	118±1.91	4.56	0.36	97.71±1.35
F8	115±4.01	4.64	0.31	98.53±1.05
F9	120±0.24	4.01	0.32	97.42±0.95
F10	121±0.34	5.09	0.34	99.36±0.43
F11	118±1.91	5.11	0.39	94.48±0.26
F12	119±1.08	4.68	0.42	95.62±0.68

All values represent mean ± Standard Deviation, n=3

Table.4.Physical evaluation of duel tablets

Formulation	Weight variation*(mg)	Hardness** (kg/cm^2) ± Avg S.D (0.327)	Friability (%)	Drug content uniformity*** (%)
F1	301	3.12	0.62	94.82±0.81
F2	295	3.67	0.77	97.71±1.35
F3	293	3.85	0.62	98.53±1.05
F4	309	4.01	0.78	97.42±0.95
F5	305	3.91	0.59	99.36±0.43
F6	295	3.87	0.72	93.82±0.81
F7	298	3.54	0.66	95.71±0.55
F8	310	3.44	0.61	99.53±1.05
F9	305	3.91	0.72	91.42±0.95
F10	305	4.09	0.84	93.36±0.73
F11	309	3.81	0.79	94.48±0.86
F12	291	3.56	0.62	99.62±0.48

All values represent mean ± Standard Deviation, n=3

Dissolution testing of compressed matrix core tablet: From the dissolution studies, it could be observed that the formulations containing 1: 4 drug to polymer ratio showed good drug release retarding ability in a controlled manner for more than 15 hrs depending upon the polymer type. Drug release profiles of duel tablets were shown in Figures 1 to 3. The drug release was generally observed to be linear matrix core part of duel tablet. This type of release profile from hydrophilic matrices is attributable to synchronization between swelling and erosion of the polymer maintaining a constant gel layer (Colombo, 2000).

As per the figure 3 eudragit based matrices have exhibited significantly more drug release- retarding effect than the rest of studied formulations. The results showed that the sustained release effects of eudragit matrices were the best among the formulations studied. Relatively less swelling capacity and slow erosion of the matrix could be the reason for the above observed phenomenon. The release profiles are characterized by initial burst release within a few minutes followed by a slow release period. Upon contact with the dissolution media, the large tablets quickly disintegrated into the fast-releasing phase and the matrix core tablet. The rapid tablet disintegration was due to the presence of super disintegrating agents, which swells very quickly when in contact with water due to extensive swelling, wicking action and porous net work. After this initial rapid drug release phase, the slow release phase was extended to varying extents depending on the composition of the matrix core, in particular, the type and concentration of the polymer. The ability of the polymers especially HPMC particles to hydrate and form a gel layer around a core are well known and is essential to sustaining and controlling the release of a drug from a matrix (Reza, 2003).

Identification of drug release mechanism: Experimental data was fitted to zero-order, first order, Higuchi and Korsmeyer–Peppas models. The results were shown in the figures 4 to 7. In view of the results, it was proposed that these matrices released drug predominantly by coupled diffusion and erosion mechanisms (Colombo, 1990). But looking at the very less variation in the r2 values, the analysis of applying these models are purely empirical.

Results of FTIR: The IR spectrum of pure KTM shows a peak at 3446.79 cm-1 which is attributed to the N-H and NH2 stretching and peaks at 1469.76 cm-1, 1490.97 cm-1 are due to C=C aromatic and aliphatic stretching, peak at 1381.03cm-1 is due to –C-N vibrations, peak at 1049.28 cm-1 is due to –OH bending confirms presence of alcoholic group, peaks at 702.09, 725.23, 763.81 and 798.53 cm-1 confirms the C-H bending (aromatic). Hence, it is thus, conforms the structure of drug KTM (figures from 8 to 12). From the examination of the recorded IR spectral data, it can be seen that all the characteristic peaks of the drug are also seen in the IR spectra of the physical mixture and some more peaks were observed with physical mixtures, which could be attributed to the presence of polymers (figure 12). These results indicate that there is no interaction between the drug and polymers taken up for the investigation.

Results of the stability studies: Results of the stability testing were tabulated in table 5. It is quite evident that there is no significant difference in the cumulative percent drug before and after storage. Furthermore, the physic-mechanical properties were maintained during the storage. The photographs shown in 1 and 2 were taken after two and half years after compression.

Table.5. *In vitro* drug release stability studies of compressed core matrix (1:4 KTM:HPMC)

Time (hrs)	Before storage	After 3 months	After 6 months
0	0.00±0.00	0.00±0.00	0.00±0.00
2	8.12±0.21	7.54±0.05	7.37± 0.15
4	28±0.37	27.42±0.21	26.46±0.16
5	30.15±0.52	29.85±0.63	27.50±0.19
8	38.92±0.12	37.35±0.31	35.94±0.37
12	60.17±0.28	58.79±0.45	58.19±0.09
15	62.20 ±0.21	61.12 ±0.28	60.31±0.24

The drug content of the formulation before storage, after three months and six months found to be 98. 61± 1.73, 96.34 ± 2.25 and 93.61± 1.82 respectively

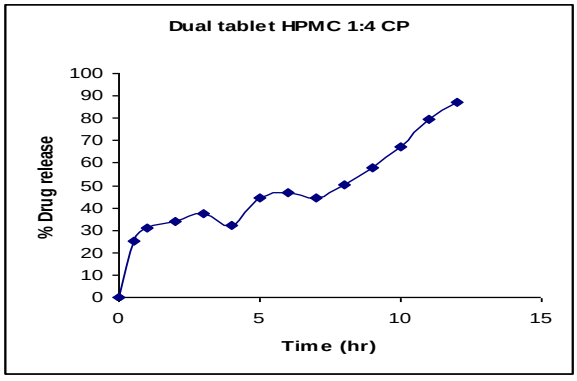

Figure.1. *In vitro* Drug release profile of Dual tablet (HPMC)

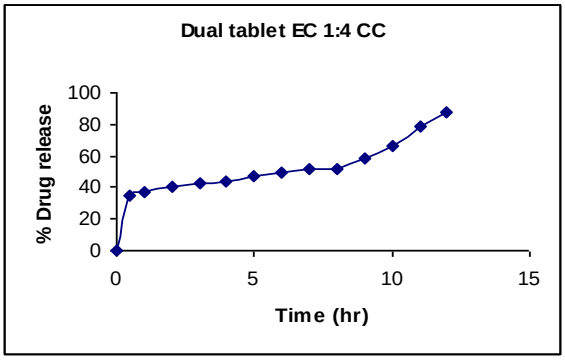

Figure.2. *In vitro* Drug release profile of (EC

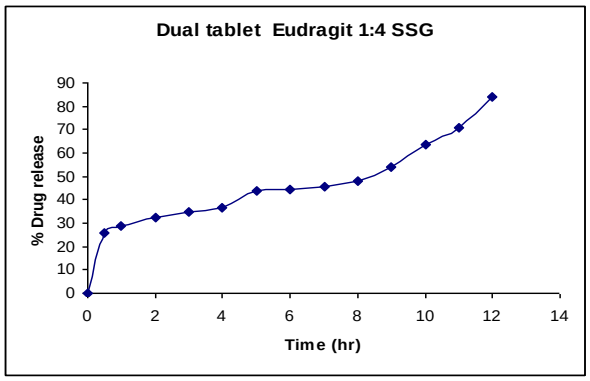

Figure.3. *In vitro* Drug release profile of optimized dual tablet (Eudragit)

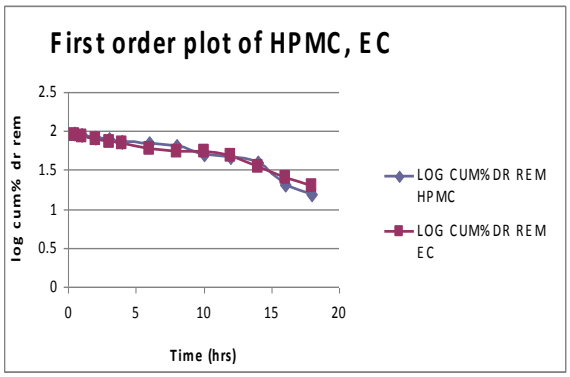

Figure.4.First order plot of HPMC, EC

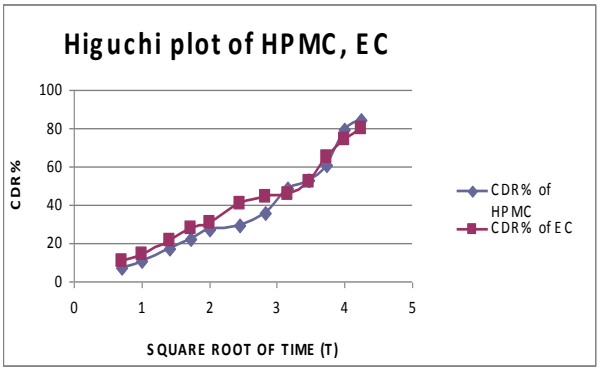

Figure.5.Higuchi plot of HPMC, EC

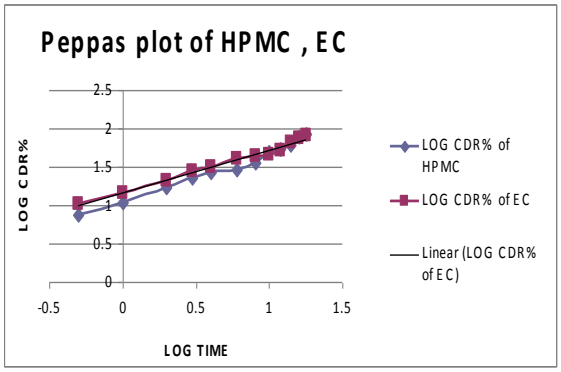

Figure.6.Peppas plot of HPMC, EC

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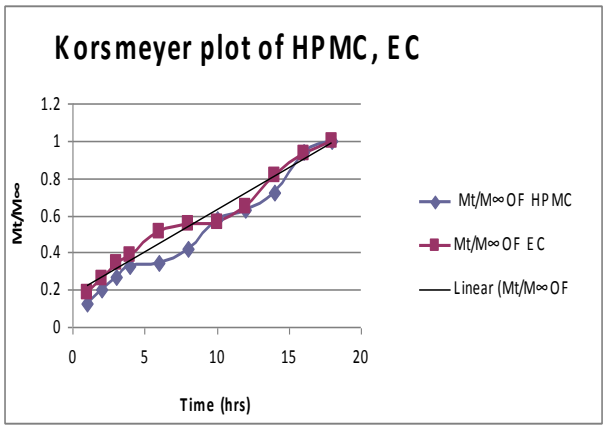


Figure.7.Korsmeyer plot of HPMC, EC

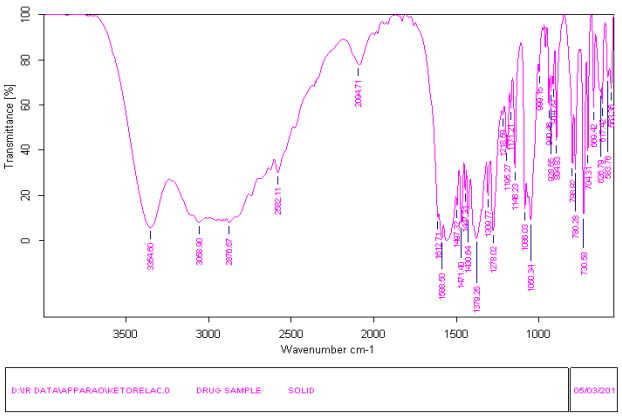


Figure.8. FT-IR spectra of KTM

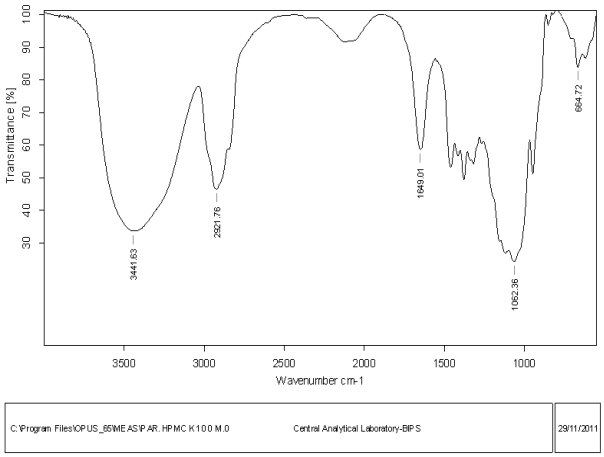


Figure.9.FT-IR spectra of HPMC

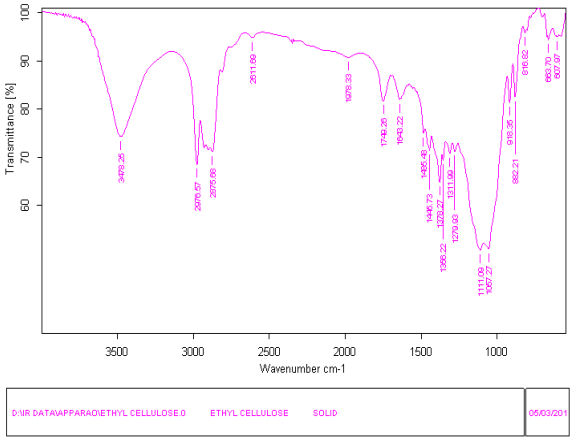


Fig.10. FT-IR spectra of EC

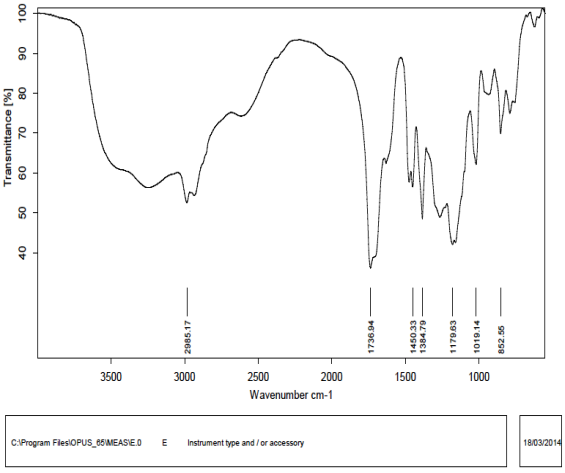


Figure.11.FTIR Spectra of Eudragit L 100-55

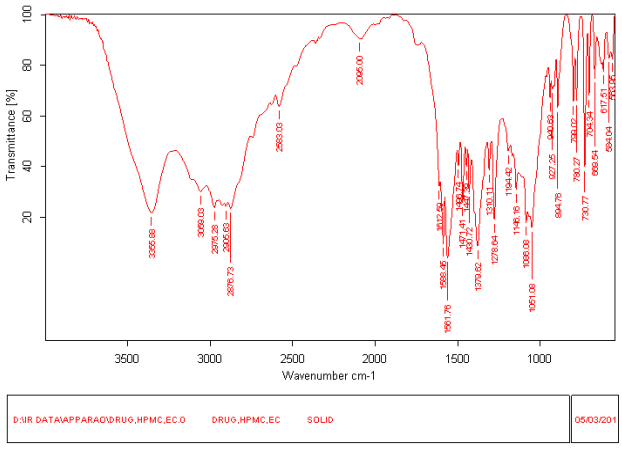
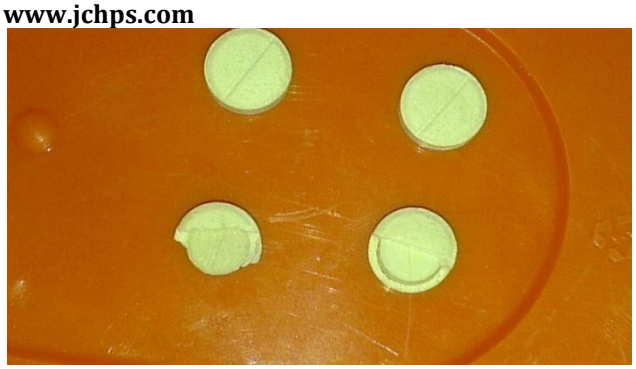


Figure.12.FT-IR spectra of KTM, HPMC, EC, Eudragit



Photograph.1.Showing dual tablets with core Tablet

Photograph.2.Liberation of core tablet after breaking of coat material

CONCLUSION

A dual-component oral compressed core matrix tablets were prepared for achieving a quick/slow delivery of the drug, characterized by an initial quick release phase, corresponding to the drug contained in the external layer, followed by a phase of slow release, corresponding to the drug from the central core tablet. Quick release provides the immediate release of fraction of total dose and was achieved using super disintegrating agents This fraction of the drug that contained in the outer coat was released within few minutes, while controlled release dose was released in a sustained manner up to about 15 hours. All the types of the polymers, (HPMC, EC and Eudragit), after the disintegration of the outer coat system, were able to modulate the release of the drug for a prolonged period of more than 12 hours.

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