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DEVELOPMENT OF SINGLE UNIT FLOATING-PULSATILE SITE SPECIFIC DRUG DELIVERY SYSTEM FOR CHRONOTHERAPEUTIC RELEASE OF ACECLOFENAC.

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ABSTRACT: Chronopharmaceutics is a branch of pharmaceutics devoted to the design and evaluation of drug delivery systems that release a bioactive agent at a rhythm that ideally matches the biological requirement of a given disease therapy. A major objective of chronotherapy in the treatment of several diseases is to deliver the drug in higher concentrations during the time of greatest need according to the circadian onset of diseases or symptoms..

The main objective of the present study was to develop single-unit floating-pulsatile drug delivery system for obtaining no drug release during floating and in the proximal small intestine followed by pulsed drug release in distal small intestine to achieve chronotherapeutic release of aceclofenac for treatment of rheumatoid arthritis, osteoarthritis, spondylytis and to improve the patient compliance.

Keywords: Chronopharmaceutics, floating-pulsatile, rheumatoid arthritis, single-unit.

INTRODUCTION

Recent studies in the area of oral controlled drug delivery include novel approaches, which prolong the GRT and Chronotherapeutic delivery system which release the drug in a pulsatile fashion, is recently gaining much attention worldwide. Pulsatile drug delivery system are characterized by two release phases, a first phase with no or little drug being released, followed by a second phase, during which the drug is released completely within a short period of time after the lag time[1].

Various diseases like asthma, hypertension, and arthritis show circadian variation, that demand time scheduled drug release for effective drug action for example inflammations associated with morning body stiffness, asthma, and heart attack in early hours of the day. Result of several epidemiological studies demonstrates the elevated risk of several pathologies during a 24 h cycle. Specifically, symptoms of rheumatoid arthritis and osteoarthritis, dyspnoea and epilepsy appear to have a peak during the night or early in the morning. Ischemic disease such as angina pectoris and myocardial infarction, and manifested more frequently during these times. Blood pressure which arises notably just before waking up is usually responsible for these attacks. Aceclofenac was chosen as a model drug, which is effective for preventing the time related occurrence of rheumatoid arthritis and osteoarthritis.[2] Aceclofenac was widely accepted as a NSAID agent.[3] So Aceclofenac is a typical example of drug, which is used in the therapy of symptoms or disease as described. However for such cases, conventional drug delivery system are inappropriate for the delivery of Aceclofenac, as they cannot be administered just before the symptoms are worsened, because during this time patient are asleep.[4,5]

To follow this principle one must have to design the dosage forms so that it can be given at the convenient time for example bed time for the above mentioned diseases with the drug release in the morning. Using current release technology, it is possible for many drugs oral delivery for a pulsed or pulsatile release, which is defined as the rapid and transient release of a certain amount of drug within a short time-period immediately after a predetermined off-release period.

Chronotherapeutical devices based on multiphase drug release were achieved by using a three layer tablet while similar devices were also developed. Time controlled coating system was also developed including single and multiple unit dosage forms [6]. The concept of the multiple unit dosage form was introduced in the early 1950s. These solid oral dosage forms consist of a multiplicity of small discrete particulates, which include mini tablets, pellets and granules[7]. These systems provide flexibility during formulation development and gives therapeutic benefits to patients. A significant advantage of multiparticulates is that they can be divided into desired doses without making formulation or process changes. They can also be blended to deliver simultaneously incompatible bioactive agents or particles with different drug release properties. Furthermore, these dosage forms are less susceptible to dose dumping than the reservoir or matrix type, single unit tablet since the drug release profile does not depend on the drug release properties of a single unit[8].

Single unit dosage forms are defined as oral delivery systems that consist of one unit that contains a single dose of the drug and is intended to be administered singularly. Many single unit dosage forms have been developed for the modified release of bioactive materials. The most widely investigated example is the monolithic matrix based tablet. The advantages of this dosage form include high drug loading and the availability of well characterized and cost-effective production methods. Drug release from these systems is controlled by a variety of mechanisms, including drug diffusion, tablet erosion, matrix swelling or a combination of these mechanisms. Film coated and osmogen controlled single unit dosage forms have also been studied for modified release applications. Single unit includes Capsules, Coated tablets, Osmotic Pumps, Insoluble matrix tablets, soluble matrix tablets, degradable matrix tablets and ion exchange resins.

MATERIALS

Aceclofenac was chosen as a model drug (Gift sample from Unique Chemicals Division of J.B.Chemicals & Pharmaceuticals Ltd, Mumbai).Microcrystalline cellulose (Alpha chemicals laboratories) was used as a spheronizing agent. Eudragit S100 received as a free gift sample from Degussa Pharma, was used as enteric coating agent. Sodium bicarbonate (Qualigens Fine Chemicals, Mumbai) was used as an effervescent agent with HPMC K100 M, HPMC K4M, HPMC K15M (free gift sample from COLORCON Asia Pvt. Limited, India). PVP K-30 (Alpha chemicals laboratories) was used as a binder. All other reagents were of analytical grade.

EXPERIMENTAL

a) Preparation of triple layer tablets

All ingredients of each layer shown in table 1 was weighed properly and passed through a 22 mesh standard sieve. The ingredients of first layer, second layer and third layer were mixed separately in mortar and lubricated with magnesium stearate (1% w/w). Powder mixture of first layer was transferred manually into the die, and then powder mixture of second layer was transferred over the first layer, finally after addition of the third layer in to the die, the total die content was compressed with 12 mm diameter flat faced punch tooling tablet press (Lab Press).

Preparation of dry coated floating-pulsatile release tablets

Dry coated floating pulsatile release tablets were prepared by using compression coating method. Initially, core tablet of aceclofenac was prepared and coated on compression machine.

c) Preparation of core tablets (CT)

All ingredients of core tablet given table 2 were weighed and passed through 22 mesh standard sieve. Resultant powder was mixed thoroughly in mortar and lubricated with magnesium stearate (1 % w/w). A 200 mg powder was weighed and transferred manually in to die and compressed by using 8 mm diameter flat faced punch tooling tablet press. (Lab Press)

Table 1: Composition of Triple Layer Tablet Formulations.

F	Layer	SBC	CA	MCC pH102	DCP	EC	HPMC K4 M	MS	Aceclofenac
F1	I	10	2	35	126	50	-	2	-
	II	-	-	40	58	-	-	2	100
	III	-	-	40	83	-	100	2	-
F2	I	20	3	35	115	50	-	2	
	II	-	-	40	58	-	-	2	100
	III	-	-	40	83	-	100	2	
F3	I	30	4	35	104	50	-	2	
	II	-	-	40	58	-	-	2	100
	III	-	-	40	83	-	100	2	
F4	I	40	4	35	94	50	-	2	-
	II	-	-	40	58	-	-	2	100
	III	-	-	40	83	-	100	2	-
F5	I	40	4	35	69	75	-	2	-
	II	-	-	40	58	-	-	2	100
	III	-	-	40	83	-	100	2	-
F6	I	40	4	35	44	100	-	2	-
	II	-	-	40	58	-	-	2	100
	III	-	-	40	83	-	100	2	-
F7	I	40	4	35	18.5	125	-	2.5	-
	II	-	-	40	58	-	-	2	100
	III	40	4	40	14	-	125	2	-
F8	I	40	4	35	18.5	-	125	2.5	
	II	-	-	40	58	-	-	2	100
	III	40	4	40	14	-	125	2	-

F= Formulation code, SBC= Sodium bicarbonate, CA= Citric acid, MCC= Microcrystalline cellulose, DCP= Dicalcium phosphate, EC=Ethyl cellulose, HPMC K4M= Hydroxypropyl methylcellulose, MS=Magnesium stearate.

Table 2: Composition of Aceclofenac core tablet formulation

Formulation	Aceclofenac	MCC pH102	DCP	SSG	Magnesium stearate
CT1	100	40	58	0	2
CT2	100	40	50	8	2

CT1= Core tablet 1, CT2= Core tablet 2, MCC= Microcrystalline cellulose, DCP= Dicalcium phosphate, SSG= Sodium Starch Glycolate

d) Dry coating of core tablets

Formulation compositions of coating layer containing varying percentage of polymers were weighed and passed through 22 mesh standard sieve. The ingredients of coating layer were mixed in a mortar and lubricated with magnesium stearate (1% w/w). Required weight of coating powder was weighed and used in two steps: first half coating powder was filled into the die and CT was placed in the center of die. CT was slightly pressed to fix the coating around and under the CT. Then rest of half coating powder was filled and compressed by using 10/12 mm flat faced punch tooling tablet press. (Lab Press)

e) Evaluation of the physicochemical parameters for complete single unit system

The tablets were evaluated for weight variation, hardness, friability, swelling characteristics, Stability study, floating ability and in-vitro drug release study. For floating study, 25 tablets were placed in 500 ml beaker containing 0.1 N HCl under stirring rate of 100 rpm. The in vitro dissolution test was performed using USP type II dissolution test apparatus. The drug release study was carried out in 0.1 N HCl for initial 8 hrs, followed by in phosphate buffer pH 6.8 for 2 hrs, each 900 ml of dissolution media, maintained at 37±0.5°C and agitated at 100 rpm. Aceclofenac concentrations were determined by UV spectrophotometry at a wavelength of 275 nm.

RESULTS AND DISCUSSION

Drug content

To evaluate a tablet potential for efficacy, the amount of drug per tablet needs to be monitored from tablet to tablet, and batch to batch. To perform the test, 10 tablets were crushed using mortar pestle. Quantity equivalent to 100 mg of drug was dissolved in 100 ml phosphate buffer pH 6.8, filtered and diluted up to 50µg/ml, and analyzed spectrophotometrically at 275 nm. The concentration of drug was determined using standard calibration curve[8].

Buoyancy determination (Figure-1)

The buoyancy test of triple layer tablet and floating pulsatile release tablet was studied by placing them in 500 ml beaker containing 0.1 N HCl, then tablet from same batches were placed in dissolution test apparatus containing 0.1N HCl, maintained at 37±0.1◦C and agitated at 100 rpm. The floating onset time (time period between placing tablet in the medium and buoyancy beginning) and floating duration of tablet was determined by visual observation[9].

Figure 1. Upper view of in vitro buoyancy a) F23, b) F26, c) F30 formulations

Invitro Dissolution Study (Figure-9)

Invitro dissolution test was performed using USP type II dissolution test apparatus. The drug release study was carried out in 0.1 N HCl for initial 8 hrs, followed by in phosphate buffer pH 6.8 for 2 hrs, each 900 ml of dissolution media, maintained at 37±0.5°C and agitated at 100 rpm. Periodically 5 ml samples were withdrawn and filtered through whatman filter paper No. 33 and samples were replaced by its equivalent volume of dissolution media. The concentration of Aceclofenac was measured by UV spectrophotometrically (Jasco V-550) at 275nm for acidic and basic media.[10].

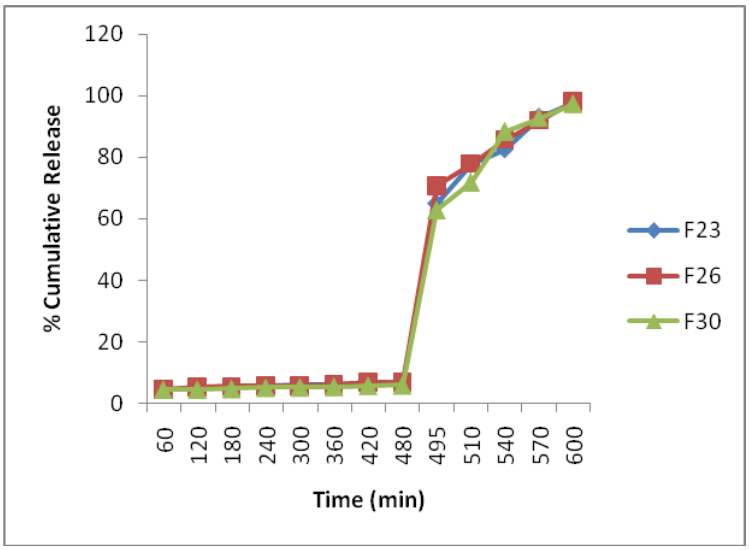

Figure 9. In vitro release profile of Aceclofenac from F23, F26, F30 Formulation for initial 480 min in 0.1 N HCl followed by 120min in phosphate buffer pH6.8

Swelling Characteristics (Figure-2)

To evaluate the water penetration characteristics, the tablets were exposed to 500 ml distilled water in three different beakers for 6 h, and then evolution of tablet surface area was carried out by recording the change in diameter and thickness of the tablets. Change in surface area of the tablets was calculated by using following formula[11].

$$SA = 2\pi r^2$$

Where, SA = Surface area and r = Radius of tablet

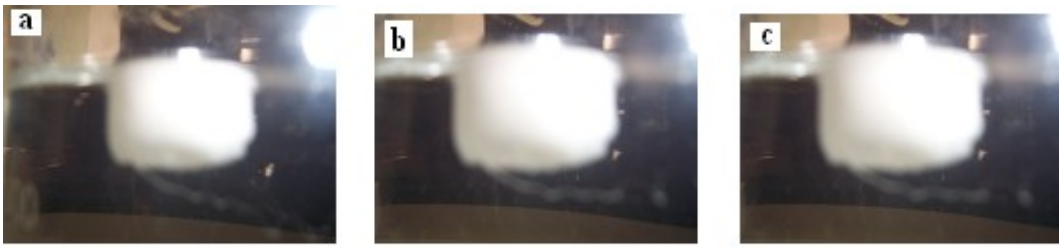

Figure 2. Side view of swelled tablet after 6 h a) F23 b) F26 c) F30 formulations.

Stability Study (Figures-3, 4, 5, 6, 7 and 8)

The fabricated floating pulsatile tablet formulations were subjected for stability study at room temperature and 50^0 C for three months. Then product evaluated for, buoyancy, drug content and invitro dissolution test and appropriate results obtained.[12].

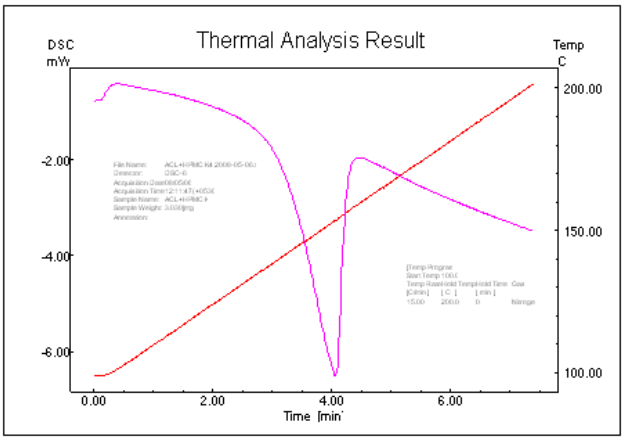

Figure 3. DSC thermogram of mixture of Aceclofenac+ HPMC K4M (1:1)

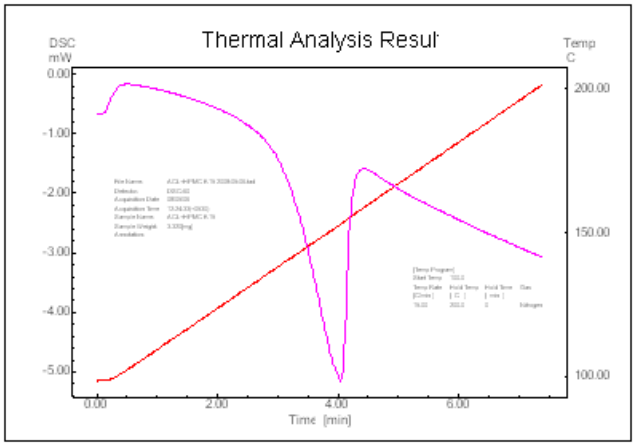

Figure 4. DSC thermogram of mixture of Aceclofenac+ HPMC K15M (1:1).

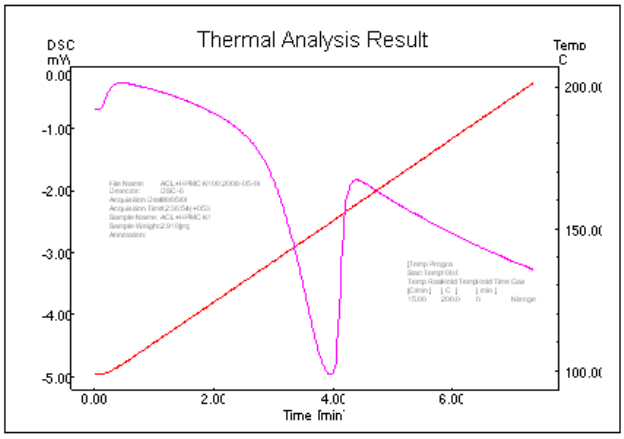

Figure 5. DSC thermogram of mixture of Aceclofenac + HPMC K100M (1:1).

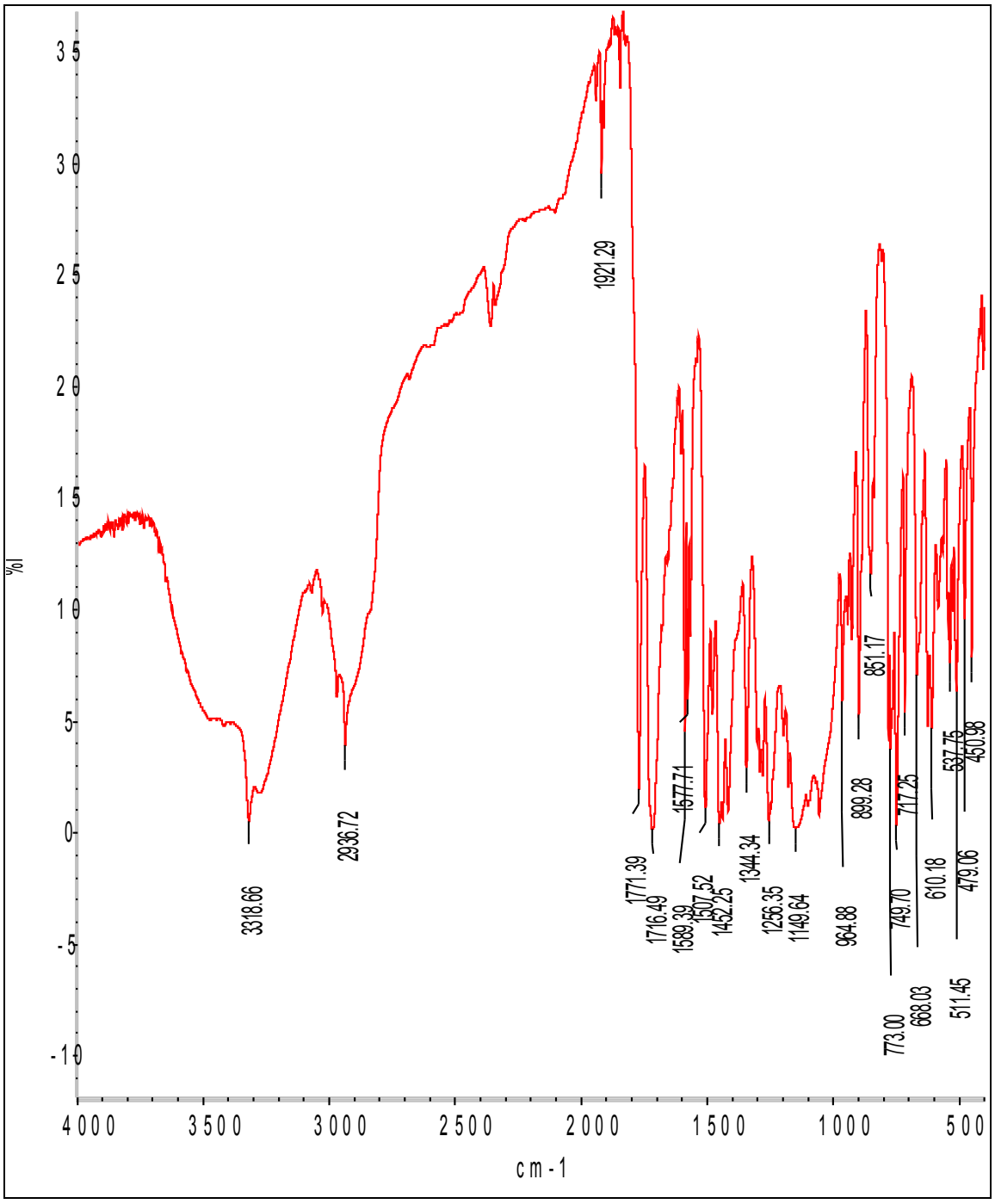

Figure 6. IR spectra of mixture of Aceclofenac + HPMC K4M

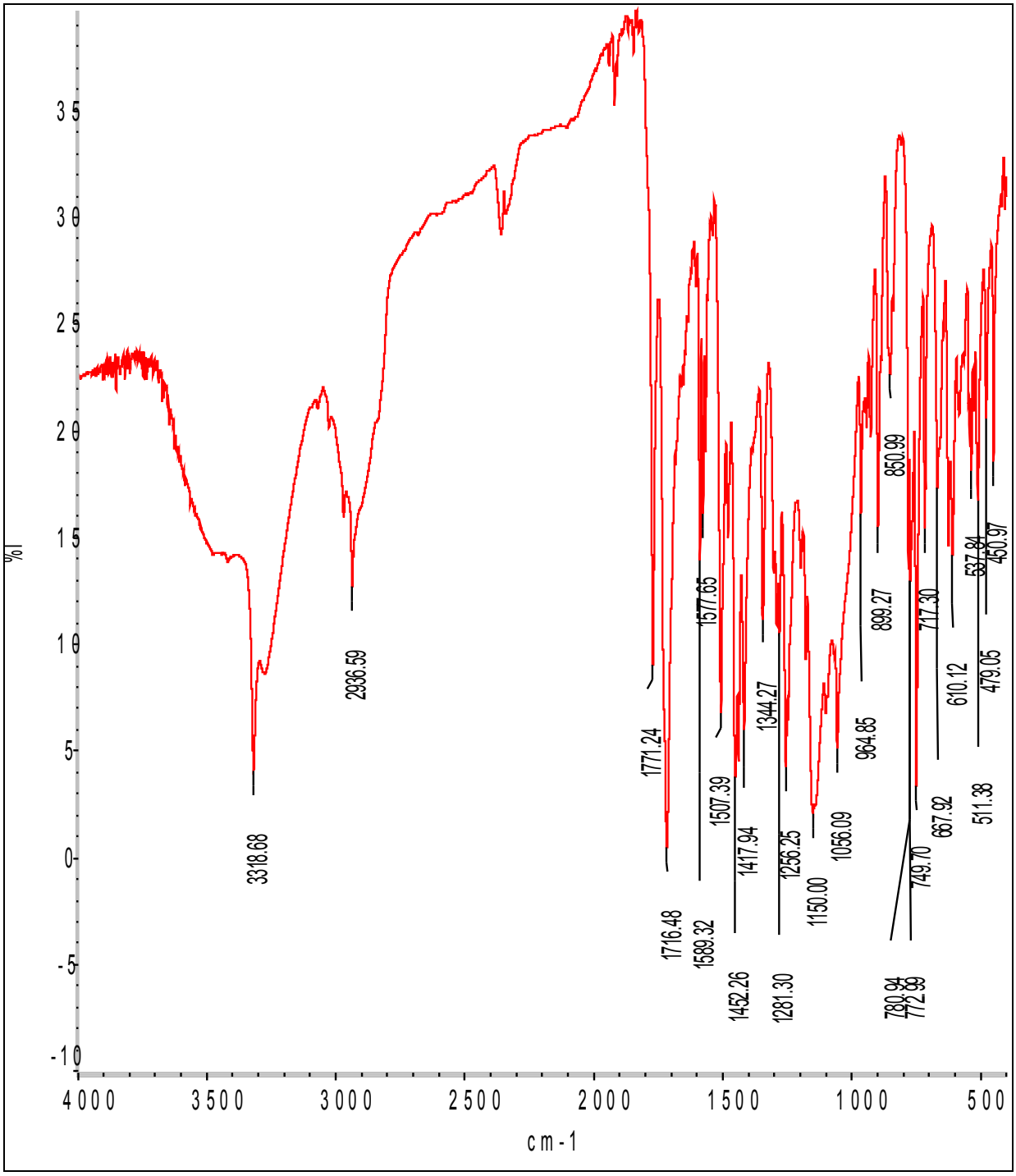

Figure 7. IR spectra of mixture of Aceclofenac + HPMC K15M (1:1).

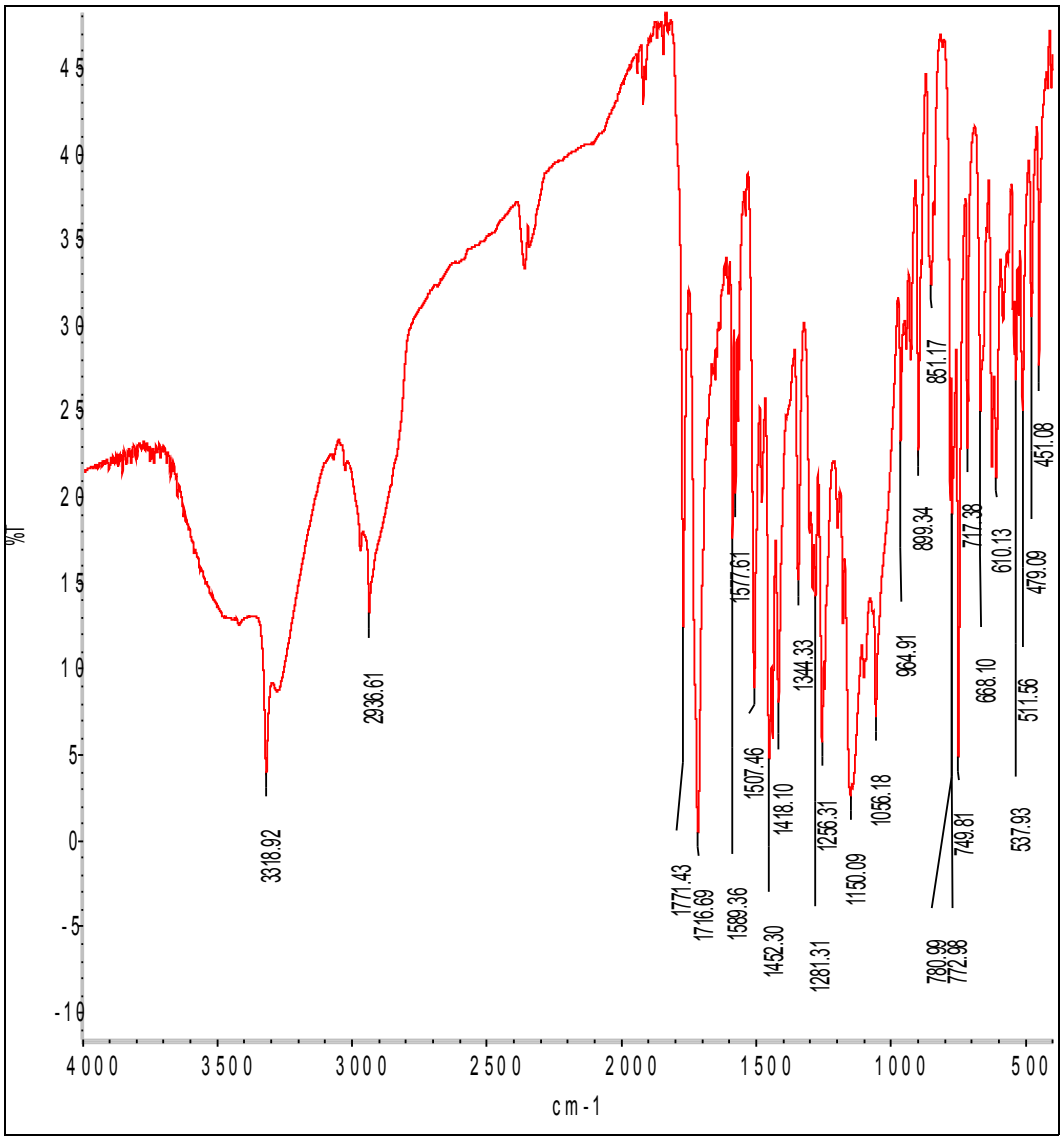

Figure 8. IR spectra of mixture of Aceclofenac + HPMC K100M (1:1)

CONCLUSION

From the present work it can be **concluded** that, dry coating of drug is necessary for providing pulsatile release pattern. The polymer coating level and amount of polymer playes a major role for providing buoyancy and pulsatile release pattern. At the same time experimentally it was found that the viscosity of polymer did not play any major role.

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