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RESEARCH ARTICLE

Evaluation of Complexed Starch-Urea-Citrate as A Novel Super Disintegrant

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ABSTRACT

The present investigation deals with the synthesis of starch-urea-citrate complex polymer by gelatinizing starch slurry with urea and citric acid. The formed starch-urea-citrate (SUC) polymer was found to be colorless and free flowing powder. Fast disintegrating tablets of ofloxacin were prepared using different concentrations of starch-urea-citrate (7.5-30% w/w of tablet) and evaluated for both pre and post compression studies. The results of granular micromeritic properties like bulk density, angle of repose, Carr's index and hausner's ratio showed that all the formulations possessed good flow properties, uniformity and compressibility. The complexation of SUC synthesis and also the compatibility between ofloxacin and the polymer were confirmed by IR spectroscopy. The compressed tablets showed good hardness (3.5-4kg/cm^2) and friability values < 0.5% with uniformity in drug content within the range of 99.2 to 100.2 %. The disintegration time of all the formulations was less than one minute. From the results, it was observed that with increments in starch-urea-citrate concentration in the formulations, there was a decrease in the values of wetting time and the disintegration time. The optimized formulation showed a complete *in-vitro* drug release within 40 min. as compared to the commercial product. Thus it was made evident that the starch-urea-citrate could be used as an excellent super disintegrant.

KEY WORDS: Oro-dispersible tablets, Starch-Urea-Citrate, Ofloxacin, Super disintegrant.

INTRODUCTION

Most of the pharmaceutical formulations for oral administration are formulated for direct ingestion, for chewing, for prior dispersion and some of them are absorbed in mouth. Many patients express difficulty in swallowing tablets and hard gelatin capsules, slow onset of drug release and non-compliance. The rapidly disintegrating tablet or oro-dispersible tablets overcome all the above problems associated with conventional dosage forms and thus offer an alternative form of oral medication, which provide patients with a more convenient means of taking their medication[1]. Addition of super disintegrating agent in the formulation is one of the approaches to formulate fast dissolving tablet which contains variety of pharmaceutical active ingredients covering many therapeutic categories Starches are naturally occurring carbohydrate polymeric substances structurally composed of straight chain amylase units with branched chain amylopectin. Starches are used since a long time as excipients in pharmaceutical preparations as an efficient binder in tablet and granule formulations, disintegrant in tablet formulations, diluent in tablet, granule, capsule and powder formulations and also matrices for specialized sustained, targeted and regulated drug delivery systems. Ofloxacin is a second-generation fluoro quinolone antibiotic which is rapidly absorbed in a dose-dependent manner. It is used as an anti-bacterial for the treatment of various diseases like chronic bronchitis, pneumonia, urinary tract infections and cervical gonorrhea and is highly effective against gram positive and gram negative bacteria it is available with 100mg dose as the branded dispersible tablets. Most of the pharmaceutical formulations for oral administration are formulated for direct ingestion, for chewing, for prior dispersion and some of them are absorbed in mouth. Many patients express difficulty in swallowing tablets and hard gelatin capsules, slow onset of drug release and non-compliance. The rapidly disintegrating tablet or oro-dispersible tablets overcome all the above problems associated with conventional dosage forms and thus offer an alternative form of oral medication, which provide patients with a more convenient means of taking their medication[1]. Addition of super disintegrating agent in the formulation is one of the approaches to formulate fast dissolving tablet which contains variety of pharmaceutical active ingredients covering many therapeutic categories Starches are naturally occurring carbohydrate polymeric substances structurally composed of straight chain amylase units with branched chain amylopectin. Starches are used since a long time as excipients in pharmaceutical preparations as an efficient binder in tablet and granule formulations, disintegrant in tablet formulations, diluent in tablet, granule, capsule and powder formulations and also matrices for specialized sustained, targeted and regulated drug delivery systems. Ofloxacin is a second-generation fluoro quinolone antibiotic which is rapidly absorbed in a

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dose-dependent manner. It is used as an anti-bacterial for the treatment of various diseases like chronic bronchitis, pneumonia, urinary tract infections and cervical gonorrhea and is highly effective against gram positive and gram negative bacteria it is available with 100mg dose as the branded dispersible tablets.

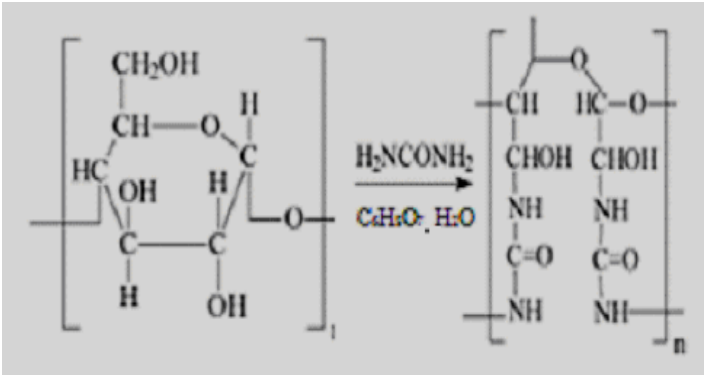
MATERIALS AND METHODS:

Ofloxacin was obtained as a gift sample from Alkem Laboratories Limited, Mumbai. Citric acid, starch, urea, purified talc, magnesium stearate and peppermint flavor were purchased from S.D Fine Chemicals Ltd, Mumbai. All other solvents and chemicals used were of AR/LR grade.

EXPERIMENTAL METHOD

I. PREPARATION OF STARCH-UREA-CITRATE COMPLEX:

Corn starch of 50g was dispersed in 100ml purified water to form starch slurry. Accurately weighed 12.5g of citric acid and urea respectively were dissolved separately in 400 ml of purified water and the solution was heated to boiling. While boiling, the starch slurry was added and mixed. Mixing while heating was continued for 10 minutes to gelatinize starch to form starch-urea-citrate complex. The mass formed was spread on to a stainless steel plate and dried at 80^0 C for 6-8 h. The dried polymer was powdered and passed through sieve # 85.



Synthesis mechanism of polymer matrix Starch-Urea-Citrate

FORMULATION OF FAST DISSOLVING TABLETS OF OFLOXACIN:

Formulations of fast disintegrating tablets of ofloxacin were prepared by wet granulation technique (1:1 ratio of water and ethanol) using varying concentration of starch-urea-citrate as super disintegrant, aspartame as sweetening agent, tartrazine as a coloring agent, mannitol as filler/ diluent, magnesium stearate as lubricant and purified talc as glidant as shown in Table: 1. The dough mass was prepared using drug, mannitol, SUC, tartrazine, aspartame and passed through sieve #16. The obtained granules were dried at 40 ^{0}C for 30 min. The dried granules were again resieved through #20. The granules were blended with lubricant, glidant, flavour and then compressed into tablets with 8 mm dies and punches using single rotary multistation compression machine (Rimek RSB-4 mini press, Cadmach, Ahmedabad).

EVALUATION STUDIES

1) FOURIER TRANSFORM INFRARED SPECTROSCOPY STUDIES:

The confirmation of SUC complexation and the drug-polymer compatibility studies were analysed by KBr disc method at a scanning range (400-4000cm^{-1}) using FTIR-8400S Spectro Photometer (SHIMADZU, Japan).

2) PRE-COMPRESSION STUDIES:

The granules were studied for various micromeritic properties such as bulk density, tapped density, angle of repose, Carr's index and Hausner's ratio.

3) POST COMPRESSION STUDIES:

The formulated tablets were evaluated for various un-official and official tests like

A. TEST FOR HARDNESS:

Hardness of the tablets was measured using the Monsanto hardness tester.

B. WEIGHT VARIATION TEST:

Twenty tablets were sampled randomly, average weight calculated and from which the individual weight variation determined.

C. FRIABILITY TEST:

Pre-weighed twenty tablets were placed in a plastic chambered Roche friabilator attached to a motor revolving at a speed of 25 rpm for 4 min. The tablets were then de-dusted, reweighed and percentage weight loss (friability) was calculated.

$$\text{Percentage friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

D. DISINTEGRATION TEST:

Each tablet was placed in a 100 ml of water maintained at 25ºC. The time required for the tablet to completely disintegrate in to fine particles was noted.

E. WATER ABSORPTION RATIO (R):

A piece of tissue paper (12cmx10.75cm) folded twice was placed in a petri dish (Internal Diameter-9cm) containing 9ml of water. A tablet was kept on the paper

and time required for complete wetting was measured. The wetted tablet was then re- weighed (W_a). Water absorption ratio (R) was determined by the following equation:

$$\text{water absorption ratio} = \frac{Wa - Wb}{Wb} \times 100$$

Where, W_a – weight of tablet after water absorption

W_b – weight of the tablet before absorption

Three tablets from each formulation were performed and standard deviation was also determined.

F. DRUG CONTENT ANALYSIS:

Ten tablets from each formulation batch were powdered. Powder triturate equivalent to 100mg of ofloxacin was weighed and transferred to 100 ml volumetric flask, initially about 50 ml of 0.1N HCl was added and the flask was shaken thoroughly and the volume was made up to the mark with the same solvent. Further dilutions were made and the drug content was estimated by UV-Visible spectrophotometer (Shimadzu 1700) at 293 nm against 0.1N HCl as blank.

G. *IN-VITRO* DRUG RELEASE STUDIES:

In-vitro dissolution studies of the formulations and marketed product were carried out according to USP XXIII Type-II dissolution apparatus employing a paddle stirrer at a speed of 50rpm using 900ml of pH 6.8 phosphate buffer at 37±0.5^{0}C as the dissolution medium. Aliquots of the sample were withdrawn at specific time intervals of 5 min. up to 60 min. and replaced with same volume of fresh medium in order to maintain sink condition. The withdrawn samples were diluted with 0.1N HCl suitably and analyzed by using UV-Visible spectrophotometer (Shimadzu 1700) at 293 nm using 0.1N HCl as blank.

RESULTS AND DISCUSSION:

The synthesis of starch-urea-citrate complex polymer was prepared by gelatinizing starch slurry with urea and citric acid. The formed starch-urea-citrate polymer was found to be fine and free flowing powder upon drying. The IR spectrum of starch (Figure:1) has shown characteristic peaks at 3288.40 cm^{-1} (OH stretch) indicating alcohol, 2891.10 cm^{-1}(C-H stretch) indicating asymmetric stretch, 1018.34 cm^{-1}(C-O stretch in ring) alcohol bond. The IR spectrum of urea (Figure:2) has shown characteristic peaks at 3340.48 cm^{-1}(NH stretch) indicating primary stretch, 1687.60 cm^{-1}(C=O stretch) indicating carbonyl group presence and the IR spectrum of citric acid (Figure:3)has shown characteristic peaks at 3290.33 cm^{-1}(OH stretch) indicating carboxylic acid, 2952.81cm^{-1}(C-H stretch) indicating carboxylic acid, 1737.74 cm^{-1}(C=O stretch) indicating aliphatic group presence. The IR spectrum of starch-urea-citrate complex (Figure:4) has shown the formation of polymer complex with the presence of new characteristic peaks at 3469.70 cm^{-1}(NH stretch) indicating primary amides, 2877.60 cm^{-1}(C-H stretch) indicating asymmetric stretch, 1739.07 cm^{-1}(C=O stretch) indicating aliphatic aldehydes group and 1691.46 cm^{-1}(C=O stretch) indicating amides. The IR spectrum of pure drug ofloxacin (Figure:5) has shown characteristic peaks at 1463.87cm^{-1} (C-C stretch in ring) indicating aromatics, 1712.67cm^{-1} (C=O stretch) indicating carboxylic acid, 1053.06cm^{-1}, 1145.61cm^{-1}(C-N stretch) indicating amine, 1288.36cm^{-1}(C-O stretch) indicating ester, 802.33cm^{-1}, 709.76cm^{-1}(C-X stretch) indicating alkyl halide present in it. The IR spectra of physical mixture (Drug: SUC) Figure. 6 also showed the characteristic peaks of pure drug indicating that there was no interaction between the drug and the polymer. Oro dispersible tablets of ofloxacin were prepared using different concentrations of starch-urea-citrate polymer by conventional wet granulation method. The results of micromeritic properties (Table 2) of formulated granules showed good bulk density (0.392-0.478 g/cc) with excellent flow properties [angle of repose: 20 ^{o}.8' – 23 ^{o}.42'] and compressibility values. The compressed tablets showed good hardness and friability as compared with the marketed product. All the tablet formulations showed uniformity in drug content within the range of 99.2 to 100.2 %. The disintegration time of all four formulations was less than one minute. From the results, it was observed that with increments in starch-urea-citrate concentration in the formulations, there was a decrease in the values of wetting time and the disintegration time. This part of study confirmed that the prepared starch-urea-citrate can be effectively used as super disintegrant. The comparative *in-vitro* drug release profile of all the four formulations with the commercial product depicted in the Figure: 7 showed a complete drug release within 40 min. with the formulation DTT-4 of the prepared tablet showed similar drug release profile in comparison with the marketed product.

CONCLUSION:

Starch-urea-citrate complex polymer was synthesized by suitable method. The SUC as a super disintegrant in the development of fast dissolving tablets of ofloxacin was studied and it was proved to be an opt novel super-disintegrant.

Sr. No.	Ingredients	Formulation Code (mg)			
		DTT-1	DTT-2	DTT-3	DTT- 4
1	Ofloxacin	100	100	100	100
2	Starch- Urea- Citrate	15	30	45	60
3	Aspartame	10	10	10	10
4	Tartrazine	3	3	3	3
5	Magnesium stearate	3	3	3	3
6	Purified talc	7	7	7	7
7	Peppermint oil	0.18ml	0.18ml	0.18ml	0.18ml
8	Mannitol (q.s.)	200	200	200	200

Table No.1: Batch Formulae of Ofloxacin Oro-dispersible tablets

Sr. No.	Formulation Code	Bulk Density* (g/ml)	True density* (g/ml)	Bulkiness* (ml/g)	Carr's index (%)	Hausner's ratio	Angle of repose (θ)
1	DTT-1	0.477±0.005	0.556±0.001	2.096±0.001	14.20	1.165	$20^{o}.80^{'}$
2	DTT-2	0.392±0.001	0.523±0.001	2.551±0.005	13.94	1.134	$22^{o}.31^{'}$
3	DTT-3	0.478±0.001	0.558±0.005	2.092±0.005	14.33	1.167	$23^{o}.42^{'}$
4	DTT-4	0.448±0.001	0.523±0.005	2.232±0.002	14.34	1.167	$22^{o}.22^{'}$

Table No.2: Micrometric properties of formulations

***Average of three determination** ± S.D.

Sr. No.	Parameters*	Formulation code			
		DTT-1	DTT-2	DTT-3	DTT- 4
1	Hardness (kg/cm^2)	3.5±0.288	3±0.500	3.5±0.500	3±0.500
2	Friability (%)	0.46±0.010	0.39±0.010	0.44±0.005	0.41±0.015
3	Weight variation (mg± S.D)	199±4.96	203±3.03	200±3.76	207±2.54
4	Wetting time(sec.)	95±1.00	87±1.00	73±0.57	53±1.00
5	Disintegration time (sec.)	50±1.00	48±1.00	32±1.00	27±1.00
6	Water absorption ratio (%)	75±5.00	77.5±1.25	82.5±0.76	85±5.00
7	Drug content (%)	99.3±0.300	99.2±1.42	99.6±0.70	100.2±1.20

Table 3: Post compression results of ofloxacin tablets

*** Average of three determination** ± S.D.

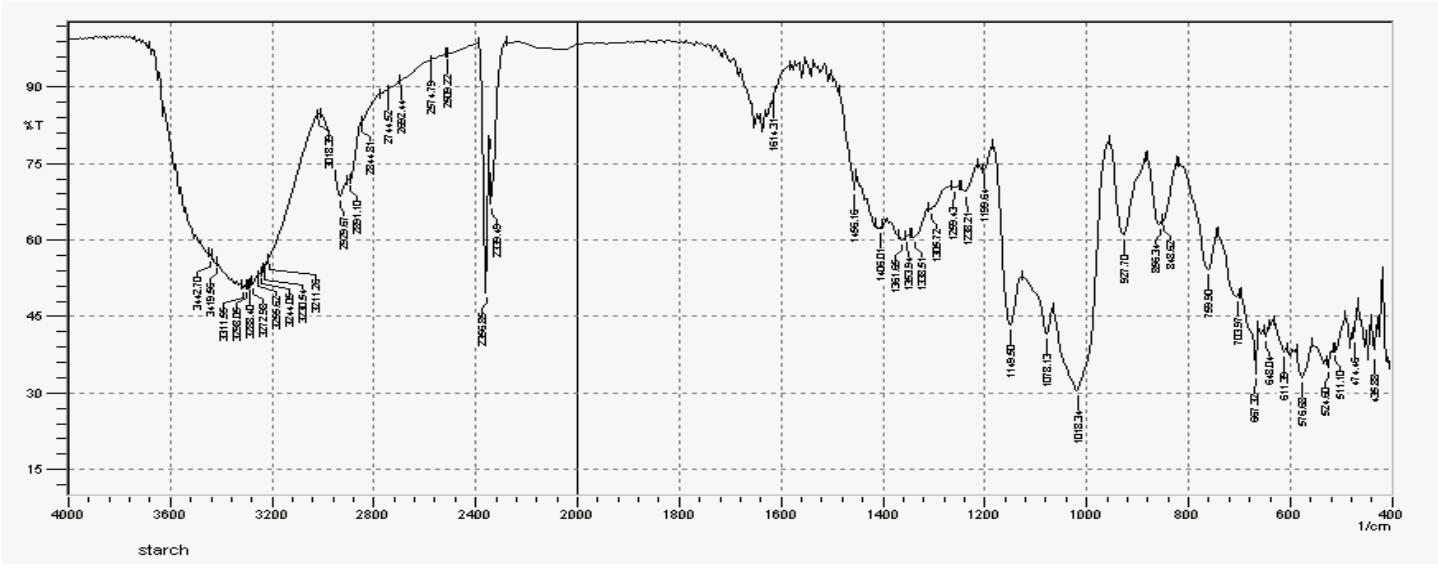


Figure No. 1: Infrared spectrum of starch

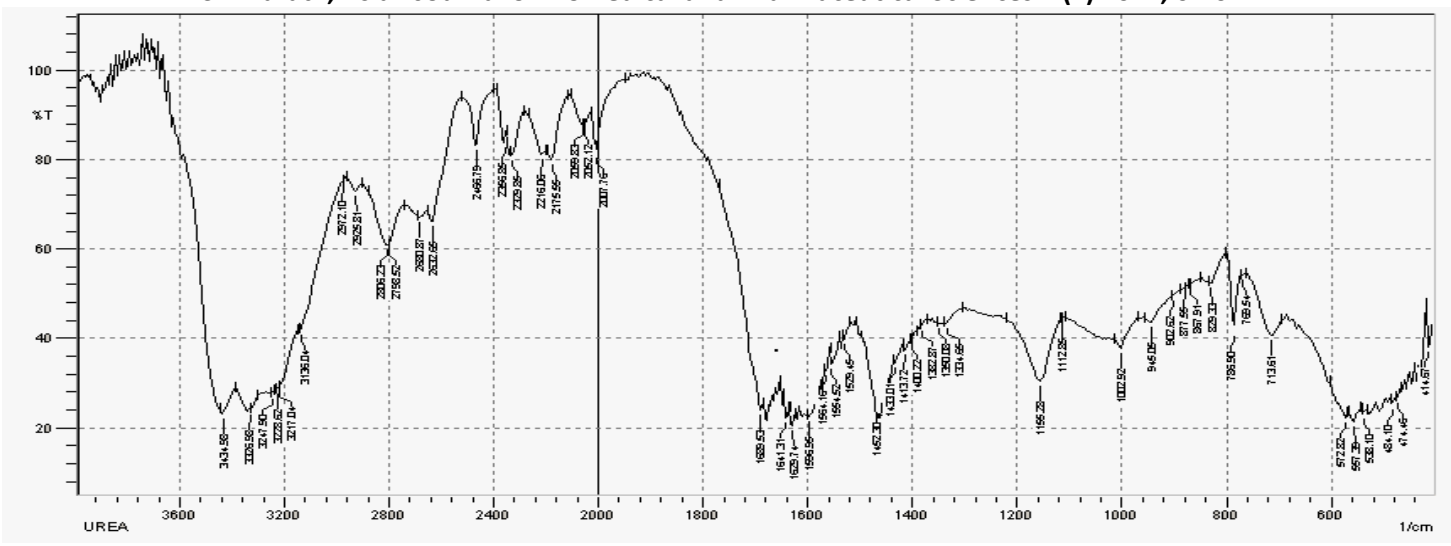


Figure No. 2: Infrared spectrum of urea

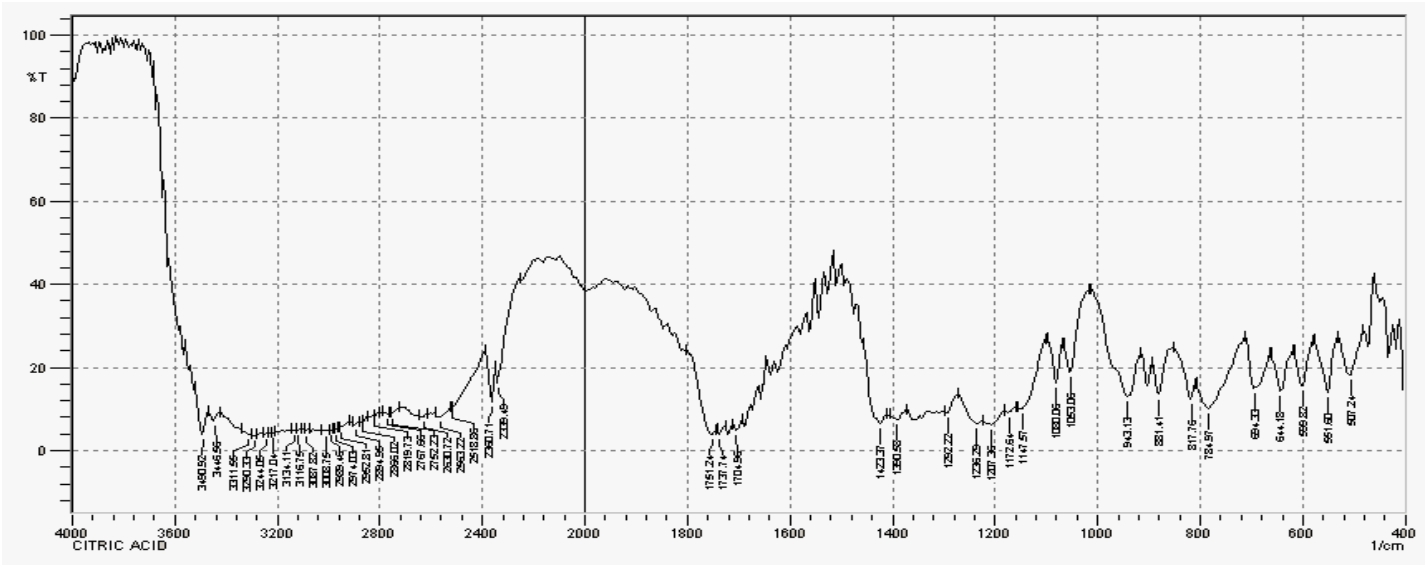


Figure No.3: Infrared spectrum of citrate

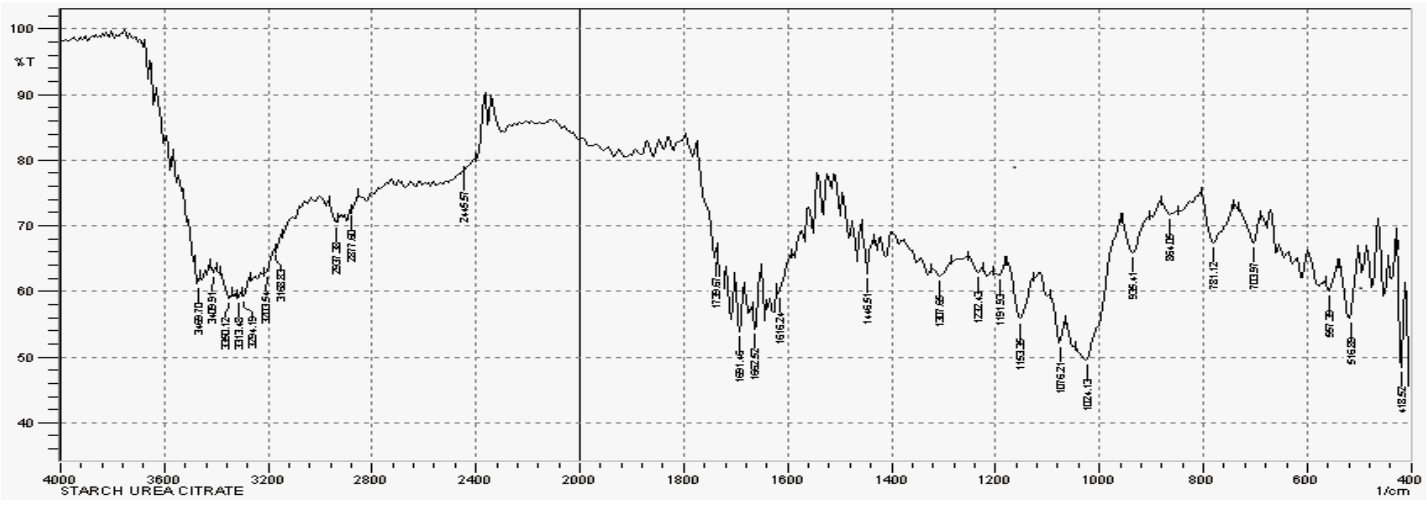


Figure No. 4: Infrared spectrum of Starch-urea-citrate complex

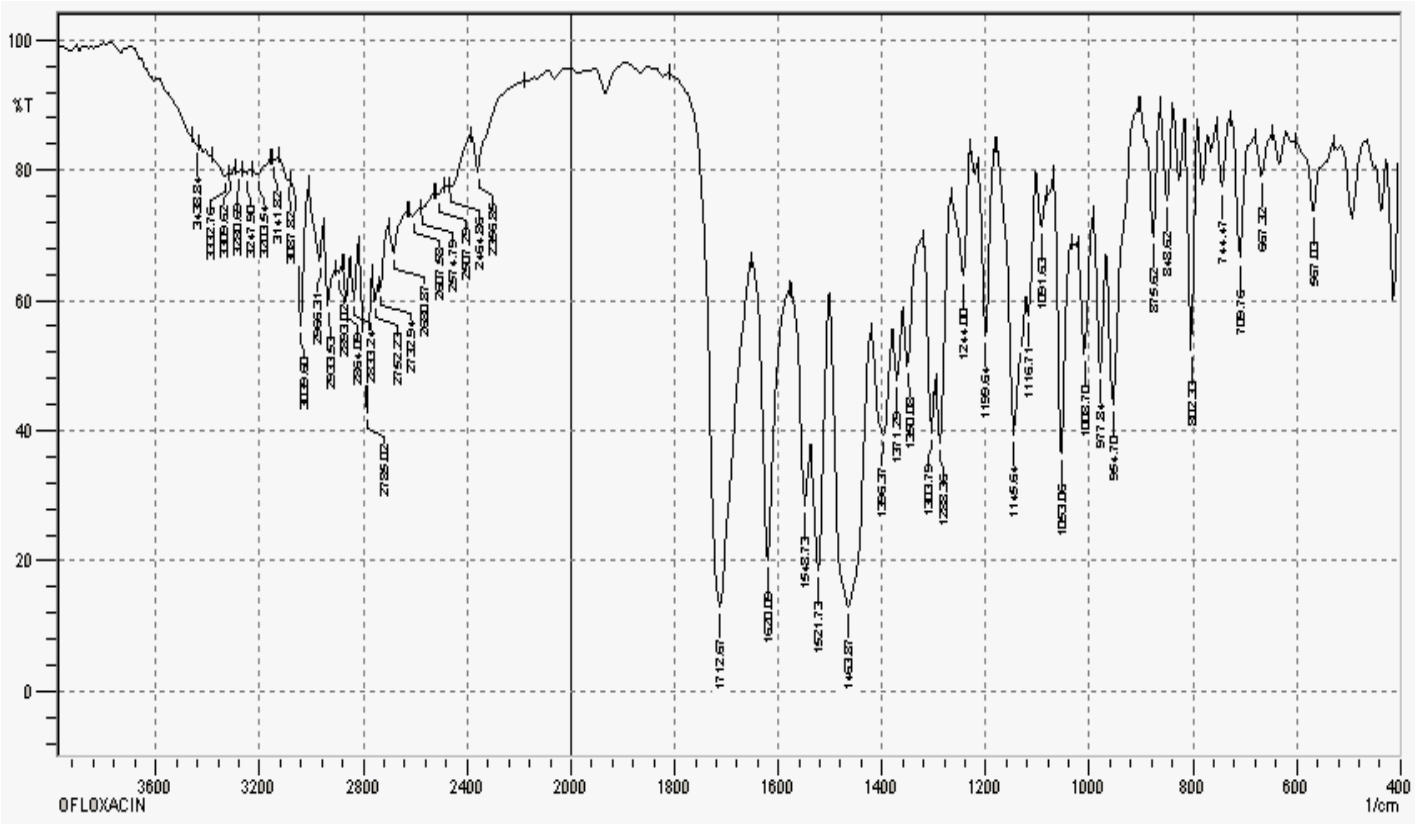


Figure No. 5: Infrared spectrum of Ofloxacin

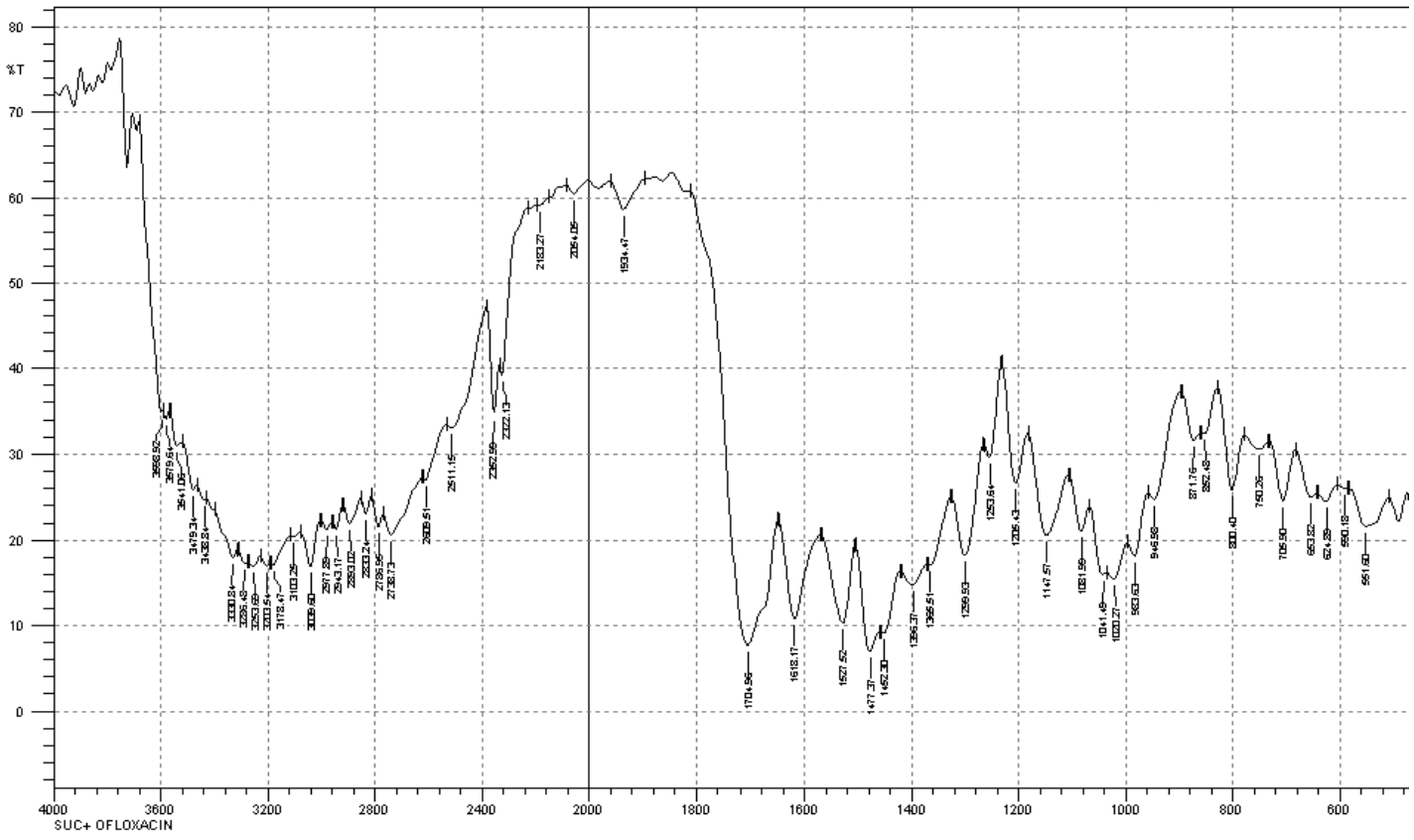


Figure No. 6: Infrared spectra of Ofloxacin + SUC physical mixture

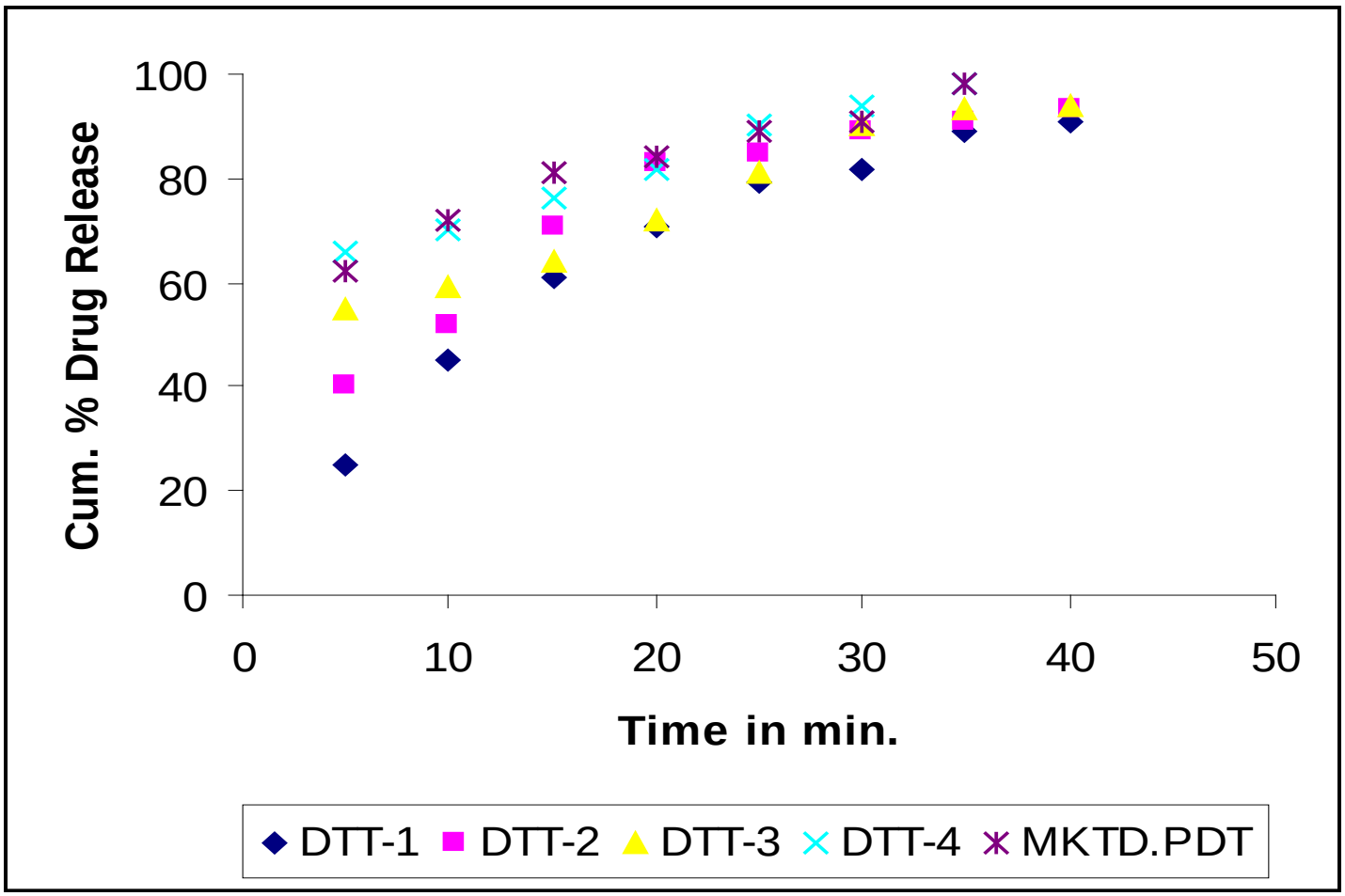


Figure No. 7: Comparative i*n-vitro* dissolution profile of formulated tablets with the marketed product

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