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Formulation, Characterization and Evaluation of Rapid Disintegrating Tablet of atifloxacin Sesquihydrate by ion exchange resin technique

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Abstract: Gatifloxacin Sesquihydrate is a Broad Spectrum Antimicrobial agent active against Gram Positive and Gram Negative Organism. It is slightly bitter in taste. In the present study an attempt has been made to prepare bitterless fast dissolving tablet of Gatifloxacin Sesquihydrate using Indion 204, Indion 214, Indion 234, Tulsion 335 (ion exchange resin) as a taste masking agent. X-ray powder diffractometry, FT-IR spectroscopy and differential scanning calorimetry were used to investigate the physical characteristics of the crystals. The tablet was prepared by Wet granulation technique with three super disintegrants e.g. sodium starch glycolate, crosscarmellose sodium and crospovidone. The granules were examined for angle of repose, bulk density, tapped density and hausner's ratio. The tablets were evaluated for hardness, drug content and friability and disintegration time. The disintegration in oral cavity was also tested and was found to be 22 sec. Also In-Vivo and In-Vitro taste Evaluation of Solid Drug: Resin Complex was carried out.
Keywords: Fast dissolving tablet, Gatifloxacin Sesquihydrate, Ion exchange resin, Super disintegrants.

Introduction

One of the attractive methods for oral drug delivery systems preferably is the use of ion exchange resins as carrier.[1] Taste masking technologies rely on preventing interaction between the drug molecule and the oral mucosal surface. By creating a physical barrier around each particle, drug substance can be prevented from going into solution and interacting directly with taste receptors. When an ionizable drug reacts with a suitable ion exchange resin the drug: resin complex formed is known as a drug resinate. Because the drug resinate is insoluble it has virtually no taste, so that even very bitter drugs lose their taste when converted into a drug resinate. With the correct- selection of the ion exchange resin, the drug resinate can be made sufficiently stable that it does not break down in the mouth so that the patient does not taste the drug when it is swallowed. However, when the drug resinate comes into contact with the gastrointestinal fluids, usually the acid of the stomach, the complex is broken down quickly and completely. The drug is released from the resinate, directly into solution and then absorbed in the usual way. The resin passes through the GI tract without being absorbed.[2] Gatifloxacin Sesquihydrate is chemically (±) 1-cyclopropyl-6-fluro-1, 4-dihydro 8-methoxy-7- (3-methyl-1-piperazinyl)-4-oxo-3-quinoline carboxylic acid Sesquihydrate. It is used as broad Spectrum Antimicrobial agent active against Gram Positive and Gram Negative Organism.[3] Taste masking is an essential requirement for fast dissolving tablets for commercial success. Taste masking of the active ingredients can be achieved by various techniques. Two approaches are commonly utilized to overcome bad taste of the drug.[4] The first includes reduction of drug solubility in saliva, where a balance between reduced solubility and bioavailability must be achieved. Another approach is to alter the ability of the drug to interact with taste receptor. Most of the bitter drugs have nitrogen atom and amine as a functional group, which is the cause of their obnoxious taste. If the nitrogen atom and functional groups are blocked by complex formation the bitterness of the drug reduces drastically. Ion exchange blocks the functional group responsible for causing the bitter taste by forming complex between ion exchange resin and the drug. Further because of the complex, the drug doesn't release in the saliva. Thus the resin reduces the drug and taste buds interaction.[5,6] In present study an attempt has been made to prepare taste masked complex of drug and these taste masked complex of drug and resin was further formulated into the mouth-dissolving tablet by wet granulation method using sodium starch glycolate, crosscarmellose sodium and crospovidone as the superdisintegrants.

Materials and Methods

Gatifloxacin Sesquihydrate was obtained as a gift sample from Jaipur pharmaceutical works Laboratories Ltd., Jaipur India. Sodium starch glycolate, cross carmellose sodium, crospovidone and Indion 204 were obtained as gift samples from Ion Exchange India Ltd., Mumbai and Thermax India Ltd., Pune, India

Preparation of drug-Resin complex.

Fixed amount of drug was mixed with different amount of powdered ion- exchange resin i.e. they were mixed at 1:0.5, 1:1, 1:1.5 and 1:2, ratios with the help of mortar and pestle. The taste masked resinate (equivalent to 200 mg of Gatifloxacin per tablet) was granulated along with diluent using PVP K 30 as a binder. The wet mass was screened through sieve no. 16 and dried at 60^0C for 30 min. The dried granules were then screened through sieve no. 40.[7]

Selection of drug-Resin complex ratio:

Four batches were prepared containing drug Resin in the ratio of 1:0.5, 1:1, 1:1.5 and 1:2.by the above-mentioned method. On the basis of the taste of the granules ratio 1:1:5 was finalized for further study.[8]

Characterization of Solid drug: resin complex:

A. Fourier Transform Infra-Red Spectroscopy study (FTIR):

Pure drug, pure resin, physical mixtures of drug-resin and drug resin complex were analyzed for Fourier Transform Infrared Spectroscopy (FTIR) using KBr disk method. Graphs are shown in Fig. 02.

B. X-ray Powder Diffraction study (XRPD):

This study was performed at Physics Department, Nagpur. Pure drug, pure resin, physical mixture of drug and resin (1:1.5) and drug resin complex were analyzed for X-ray powder diffraction (XRPD). All samples were run at (2θ) min^{-1} from 10º to 60º (2θ). X-ray Diffractograms are shown in Fig. 03.

Physical evaluation of drug-Resin granules: Granules were evaluated for angle of repose, bulk density, tapped density, Hausner's ratio.

Formulation of [bitterless] fast dissolving tablet of drug: **Resin granules**
by disintegrant addition method

Fast dissolving tablets of Gatifloxacin Sesquihydrate: Indion 204 granules were prepared using direct compression method after incorporating different superdisintegrants such as, crosscarmellose sodium (Ac-Di-Sol), crospovidone and sodium starch glycolate in different concentrations. Nine formulations of Gatifloxacin Sesquihydrate: Indion 204 granules were prepared and each formulation contained one of the three disintegrant in different concentration. Finally these granules were compressed on multiple tablet compression machine using 12 mm standard punches to give tablet weight of 600 mg. Ingredient are depicted in table no. 1

Table 1: Formulation table of batch F1-F9.

Ingredients (mg/tab)	F1	F2	F3	F4	F5	F6	F7	F8	F9
D.R.C.	500	500	500	500	500	500	500	500	500
Aspartame	10	10	10	10	10	10	10	10	10
PVP K 30	42	36	30	42	36	30	42	36	30
C.C.S.	36	42	48	--	--	--	--	--	--
Cross Povidone	--	--	--	36	42	48	--	--	--
S.S.G.	--	--	--	--	--	--	36	42	48
Menthol	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.
Raspberry Flavor	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.
Magnesium stearate	06	06	06	06	06	06	06	06	06
Colloidal Silicon dioxide	06	06	06	06	06	06	06	06	06

DRC: Drug resin complex,
CCS: Cross Carmellose sodium,
SSG: Sodium starch glycollate,
Tablets are prepared in batch of 50

Evaluation of formulated tablet[9,10,11]

Tablet Hardness

The strength of tablet is expressed as tensile strength (Kg/cm^2). The tablet crushing load, which is the force required to break a tablet into halves by compression .It was measured using a tablet hardness tester (Pfizer Hardness Tester).

Weight Variation Test

Weight variation test is done by weighing 20 tablets individually; calculating the average weight and comparing the individual tablet weight to the average.

Friability

Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche friabilator was used for the Purpose. This device subjects a number of tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at a distance of 6 inches with each revolution. Preweighed sample of tablets was placed in the friabilator, which was then operated for 100 revolutions. Tablets were dusted and reweighed. Compressed tablets should not loose more than 1% of their weigh.

Content Uniformity

Five tablets were powdered and the blend equivalent to 500 mg of Gatifloxacin Sesquihydrate was weight and dissolved in suitable quantity of water, filtered and drug content analyzed spectrophotometrically at 286.6 nm.

In vitro Disintegration Study

In vitro disintegration time was determined by dropping a tablet in a container containing 5 ml of pH 6.8 phosphate buffer. The time required for uniform dispersion of tablet was noted.

In-Vitro Release Profile of Formulated Tablets

The dissolution of Gatifloxacin Sesquihydrate tablets was carried out in basket type dissolution apparatus. The dissolution medium was 900 ml of gastric simulated fluid (without enzyme) pH 1.2 maintained at 37^0C and pH 6.8 at 37^o C. The basket was rotated at 50 rpm for 20 min. The sample of 10 ml was withdrawn after every 5 min. and its absorbance was measured at 286.6 nm.

Optimization of Formula

From the above formulations the optimized formula from Drug: Resin tablets (F6) was selected, depending upon the several factors such as less disintegrant concentration, less disintegration time and fast dissolution rate**.**Dissolution profile is given in figure no. 1

Stability Studies[12,13]

The tablets were studied for stability at 40^oC and 75% RH condition for period of three months.Each tablet was individually weighed and wrapped in aluminum foil and packed in black PVC bottle and put at above specified condition in a heating humidity chamber for 3 months. After each month tablet samples was analyzed for the hardness, disintegration time and in vitro drug release study. The results for hardness and disintegration time are shown in table 03 and that for dissolution profiles of drug resin complex tablets are shown in fig. 01.

Table 2: Evaluation of tablets

Parameters	Formulation								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Tensile strength* (Mpa)	10.12 ±0.14	9.38 ±0.33	8.94 ± 0.58	12.72 ±0.11	11.44 ±0.02	11.06 ± 0.07	12.10 ±0.05	11.91 ±0.17	11.65 ± 0.52
Friability* (%)	0.27 ±0.12	0.30 ±0.15	0.31 ±0.21	0.13 ±0.41	0.18 ±0.67	0.21 ±0.87	0.19 ±0.21	0.17 ±0.40	0.16 ±0.01
Content Uniformity* (%)	99.13 ±0.43	99.81 ±0.03	100.11 ±0.21	99.85 ±0.32	99.98 ±0.29	100.21 ±0.17	99.45 ±0.52	99.89 ±0.61	100.19 ± 0.24
Wetting time* (sec)	18.21 ±0.21	17.01 ±0.43	16.29 ±0.15	15.16 ±0.31	14.26 ±0.40	11.15 ±0.58	21.14 ±0.09	19.13 ±0.21	18.23 ±0.16
Water absorption* ratio	85.16 ±0.13	85.03 ±0.16	82.12 ±0.18	84.11 ±0.17	81.07 ±0.21	82.43 ±0.11	83.11 ±0.09	87.51 ±0.22	85.70 ±0.03

(*Represents mean ± S.D.) (n = 3)

Table 3: Comparative study of disintegration time with different methods

Test Method	Disintegration time (sec.) of tablet Formulation								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
In-vitro*	35.11 ±0.31	31.02 ±0.25	29.34 ±0.21	23.13 ±0.14	22.09 ±0.11	21.33 ±0.01	41.10 ±0.22	39.05 ±0.33	36.23 ± 0.21
In-vivo test*	40.03 ±0.12	37.12 ±0.34	34.14 ±0.21	28.01 ±0.02	27.0718 ±0.29	26.19 ±0.01	44.21 ±0.38	43.11 ±0.26	41.16 ±0.17

(*Represents mean ± S.D.) (n = 3)

Table 4: Stability study of tablet formulations

Parameters	Time in months			
	0 (initial)	**1**	**2**	**3**
Hardness* (kg/cm^2)	3.58 ± 0.08	3.60 ± 0.018	3.61 ± 0.023	3.63 ± 0.031
Disintegration time* (Sec)	21.0 ± 0.11	22.11 ± 0.23	22.15 ± 0.015	24.06 ± 0.04
Drug Content* (%)	100.21 ± 0.17	100.45 ± 0.21	100.98 ± 0.13	100.99 ± 0.33

(*Represents mean ± S.D.) (n = 3)

Figure No. 1: Dissolution profile of batch F6 (disintegrant addition method)

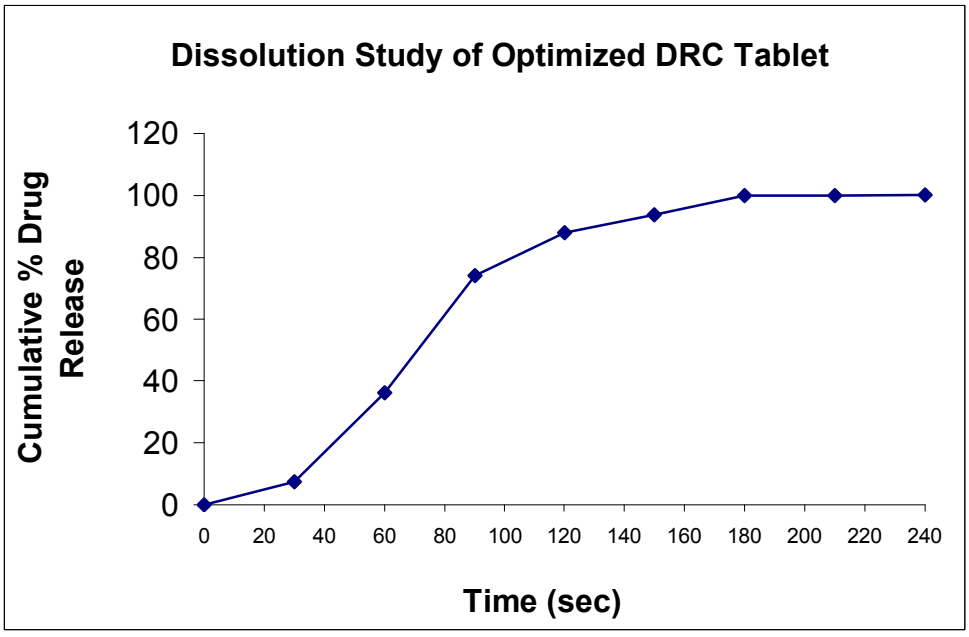
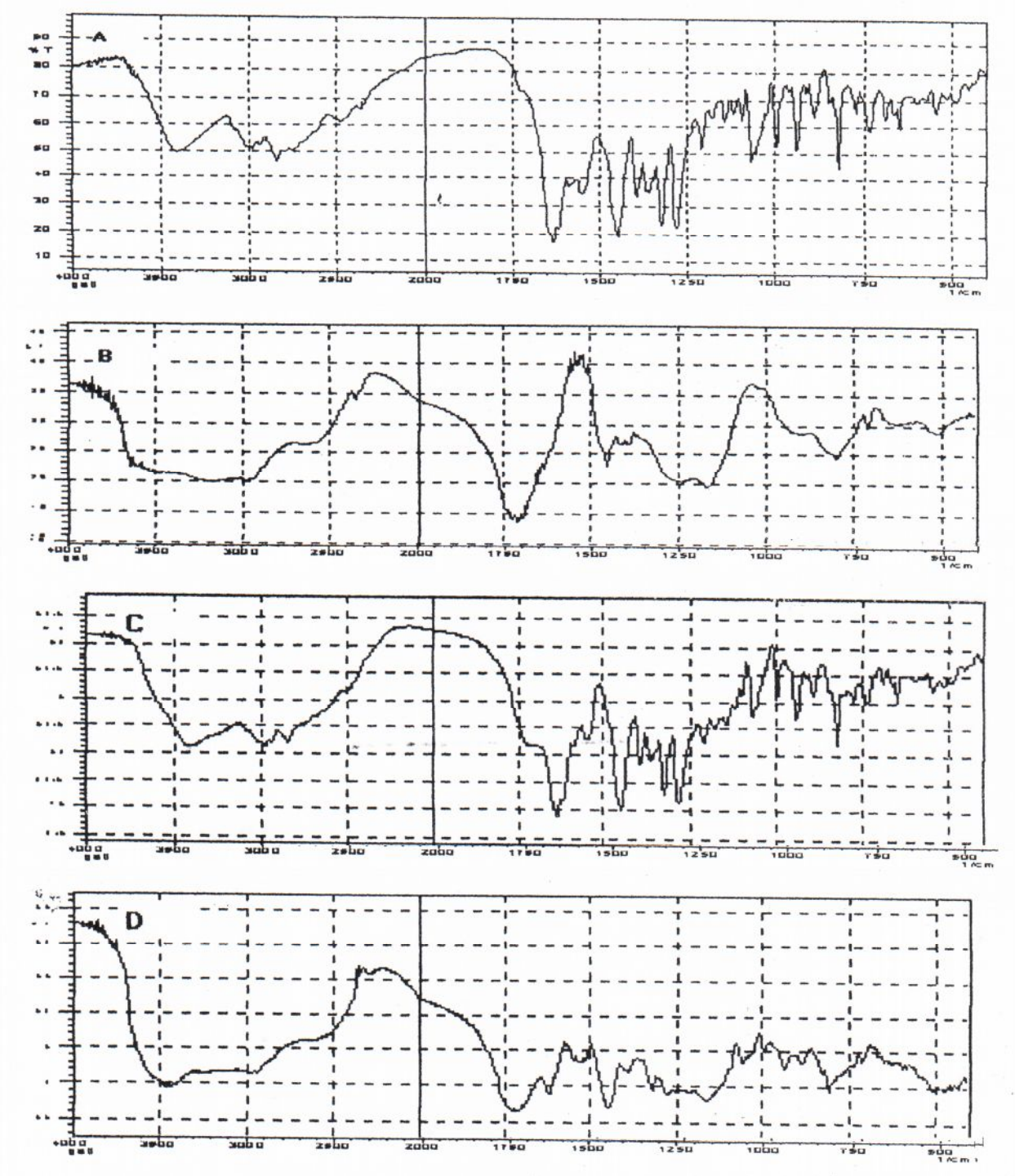
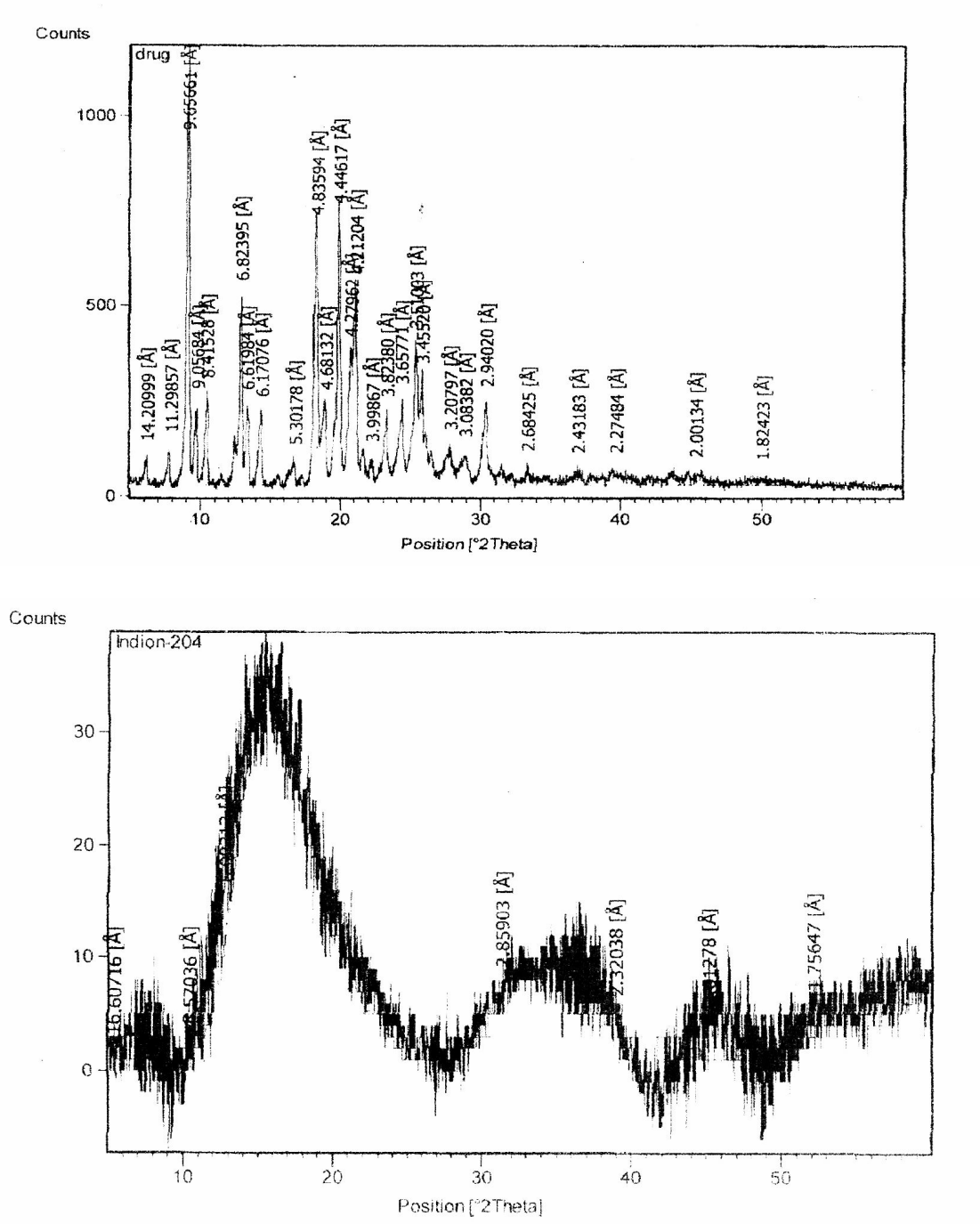


Figure No. 2: FTIR of drug-resin complex



A. Gatifloxacin sesquihydrate.
B. Indion 204
C. Physical mixture of drug and resin
D. DRC

Figure No. 3: XRPD study of drug resin complex



Results and Discussion

Indion 204 was selected for the taste masking of Gatifloxacin Sesquihydrate. The taste-masked granules of drug and Indion 204 were prepared by wet granulation method. Drug to resin ratio 1:1.5 and above shows better results as compared to other ratio. The plot of % drug loaded vs. time demonstrates that % uptake of drug from solution is highest for the ratio if 1:2 (97.16%) which is slightly higher than the % uptake for resin ratio 1:1:5 (97.10%) for this reason drug- resin ratio of 1:1:5 was selected as optimized ratio. The granules of all the batches were evaluated for different derived properties viz. angle of repose, bulk density, tapped density, compressibility index and Hausner ratio, in order to determining the flow characteristics. All the batches show satisfactory flowability, Nine formulations of drug-indion 204 granules (F1-F9) were prepared by varying the concentration of superdisintegrant.Tablets were prepared using wet granulation method. Tablets were obtained of uniform weight due to uniform die fill, with acceptable weight variation as per pharmacopoeial specification. The drug content found in the range of 99.13-100.02 % (acceptable limit) and the tensile strength

of the tablet was found between 9.38 – 12.75 Mpa. Friability of tablet was found below 1% indicating good mechanical resistance. The wetting time of formulated tablets was found in the range of 14.26- 21.14 sec and disintegration time of all batches was found in the range of 21.33-41.10 sec. Batch F-6 was selected as optimized batch containing crospovidone as superdisintegrant in 8 % concentration. It has less disintegration time of 21.33 sec. The dissolution study was carried out and 100.07% of drug release was occurring within 20 min. The stability study of optimized batch was carried out at 40^{o}C-75% RH. The tablets were found to be stable at such condition and other parameters were found to be unaffected. The formulation F6 was found to be best as this formulation showed less disintegration time, good hardness, short wetting tine and good content of active ingredient. Out of three superdisintegrant formulation containing crosspovidone (F6) shows best result. It was concluded that fast dissolving tablet of Gatifloxacin Sesquihydrate can be successfully prepared by super disintegrant addition . Taste masking with Indion 204 was also found to be effective.

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