Research Article

Formulation, Characterization and Evaluation of Taste Masked Rapid Disintegrating Tablet of Ofloxacin by Ion Exchange Resin Technique

Shailendra P. Kela*, Disha Kesharwani
Royal College of Pharmacy, Behind Pt. Ravishankar Shukl University, Dumar Talab, Mohoba Bazar, Raipur, Chhattisgarh, India.
***Corresponding author's E-mail:** kelashailendra@gmail.com

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ABSTRACT

Ofloxacin is a broad spectrum antibacterial agent active against gram positive and gram negative organism. It is very bitter in taste. In the present work an attempt has been made to develop taste masked rapid disintegrating tablet of ofloxacin using ion exchange resins (Tulsion 335, Indion 204, Indion 214) as a taste masking agent. Different drug: resin ratios were tried to prepare taste masked complex. Depending upon the taste masking and drug loading efficiency the complex with Tulsion 335 in the 1:1.5 (drug: resin) ratio was selected for the formulation of tablet. FT-IR spectroscopy and differential scanning calorimetry were used to investigate the physical characteristics of the complex. Tablets were prepared by direct compression technique using three super disintegrants viz. croscarmellose sodium, cross povidone and sodium starch glycolate. The blend was examined for angle of repose, bulk density, tapped density and Hausner's ratio. Tablets of all batches were tested for various evaluation parameters. Tablets formulated with 4.3% (F9) of croscarmellose sodium showed low disintegration time (19±1.23 sec), wetting time (25±1.75 sec) and friability (0.23±0.13%) than the other batches. The % cumulative release of drug from tablet (F9) was found to be more than 95% within 20 mins. It was concluded from the study that Ofloxacin shows optimum drug loading with Tulsion-335. Among different superdisintegrants croscarmellose sodium was found suitable.

Keywords: Ion exchange resin, Ofloxacin, Rapid disintegrating tablet, 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 ionisable 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]

Ofloxacin is chemically racemate,(±)-9-fluoro-3-methyl-10-(4-methylpiperazin-1-yl)-7-oxo-2,3-dihydro-7*H*-[1,4]oxazino[2,3,4-*ij*]quinoline-6-carboxylic acid.[3] It has an in vitro activity against a broad spectrum of gram positive and gram negative and anaerobic bacteria.[4] 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.[5] Among those, taste masking by use of ion exchange resin is most commonly used commercially.[6] 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 with drug and it not allow the drug to release in the saliva. Thus the resin reduces the drug and taste buds interaction.[7] In present study an attempt has been made to prepare taste masked complex of ofloxacin with ion exchange resins and complex was further formulated into the rapid disintegrating tablet by direct compression method using sodium starch glycolate, cross povidone and crosscarmellose sodium as the super disintegrants.

MATERIALS AND METHODS

Materials

Ofloxacin was obtained as a gift sample from Emcure Pharmaceuticals, Pune. Ion exchange resins, croscarmellose sodium, cross povidone and sodium starch glycolate were also obtained as a gift sample from Emcure Pharmaceuticals, Pune, India.

Selection of λ_{max} of drug

Accurately weighed 100 mg of ofloxacin was dissolved in sufficient amount of 0.1N hydrochloric acid in 100 ml of volumetric flask and diluted to make up the volume. From the above solution 10 ml of aliquot was withdrawn and diluted to 100 ml so as to obtain solution of 100µg/ml (standard solution). This solution was scanned between

200-400 nm so as to find out the absorption maxima of the drug.

Preparation of drug-resin complex ratio

Three ion exchange resins viz. Tulsion 335, Indion 204 and Indion 214 were used for the taste masking of the Ofloxacin. Fixed amount of drug was mixed with different amount of powdered ion-exchange resins i.e. 1:1, 1:1.5 and 1:2, ratio with the help of distilled water. At first the ion exchange resin was allowed to swell for 30 min. in distilled water and then drug is added into the resin and allowed for continuous stirring for 6 hours and kept overnight for complete complexation. Then supernatant was removed and complex was dried in a tray dryer for a period of 6 hour at 60° C and LOD was determined at a temperature of 105°C and kept below 3. The dried complex (equivalent to 100 mg of ofloxacin per tablet) was sifted through sieve no. 30.[8] To study the effect of stirring time and speed on the solubility of drug, pure drug was also stirred for 6 hours with water and it was taken as standard.

Evaluation of effectiveness of taste masking[9, 10]

The in-vivo taste evaluation consists of a double blind crossover study, carried out on a trained taste panel of healthy volunteers with sound organoleptic senses, with their prior consent. By placing complex in the oral cavity, it was held in mouth for 60 seconds by each volunteer, and the bitterness level recorded against pure drug (control) using a numerical scale. After 60 seconds, complex is spitted out and the mouth is rinsed thoroughly with mineral water. The effectiveness of taste masking was evaluated considering

+ = Slight taste masking

++ = moderate taste masking

+++ = complete taste masking

Evaluation of drug loading efficiency

The prepared resinate complex was evaluated for the drug loading efficiency. Accurately weighed 25 mg of resinate (equivalent to 10 mg of Ofloxacin) was dissolved in 100 ml volumetric flask and volume was made up to 100 ml with 0.1 N HCl. From this solution 1 ml was withdrawn in a 10 ml volumetric flask and volume was made with 0.1 N HCl and absorbance was noted, from which drug loading was calculated.

Selection of drug-resin complex ratio

Using the batch method various drug- resinate complexes were prepared with ion exchange resins in different ratio. Depending upon the taste masking and % drug loading efficiency batch C8 i.e. with tulsion 335 in the ratio 1:1.5 was selected. The batch C8 has complete taste masking with 98.25% drug loading. Batch C9 also showed good taste masking with % drug loading but there is no significant difference when compared to batch C8. So batch C8 drug-resinate complex was used for the further studies.

Characterization of Solid drug: resin complex

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

The IR spectrums of pure Ofloxacin, Tulsion 335, resinate and tablets of F9 (optimized) batch were recorded using Fourier Transform Infra-Red spectrophotometer (Varian, 640 IR) with diffuse reflectance principle. Sample preparation involved mixing the sample with potassium bromide (KBr), triturating in glass mortar and finally placing in the sample holder. The spectrum was scanned over a frequency range 4000 - 400 cm^{-1}.

B. Differential Scanning Calorimetry (DSC)

DSC is a technique for measuring the energy necessary to establish a nearly zero temperature difference between a substance and an inert reference material, as two specimens are subjected to identical temperature regimes in an environment heated or cooled at a controlled rate. Phase transition of the untreated drug and the crystals were analyzed by DSC (Universal V2.4F TA Instruments, USA and Model: SDT 2960). The samples were heated in a hermetically sealed aluminium pans. Temperature range for each sample was set from 50 to 300° C at a heating rate of 10°C/min, using nitrogen as purging gas.

Formulation of [bitter less] rapid disintegrating tablet of drug: resin complex by disintegrant addition method[10,11]

The tablet consist of resinate equivalent to 100 mg of Ofloxacin. Avicel (PH 102) and Pearlitol SD 200 were selected as diluents, different super disintegrants such as, croscarmellose sodium (Ac-Di-Sol), crospovidone and sodium starch glycolate in different concentrations. Small amount of Sucralose was added as a sweetener. All the nine batches were prepared by direct compression method using 10 mm flat punches on 16 station compression machine (CADMACH). The hardness of the tablet of each batch were tried to keep constant (6-7 kg/cm^2). The weight of the tablet of each batch was adjusted to 350 mg. Ingredients are depicted in table 1.

Evaluations of powder blend

Powder blend was evaluated for bulk density, tapped density, Hausner's ratio and sieve analysis.

Evaluation of formulated tablet [12, 13, 14]

Tablets prepared from blend were subjected to evaluation of properties including weight variation, tablet hardness, friability, thickness and *in-vitro* drug release etc.

a) Drug content (By HPLC)

Mobile Phase

Buffer: 2.72gm of monobasic potassium dihydrogen orthophosphate was dissolved in 1000 ml of water and pH was adjusted to 3.3 using ortho phosphoric acid.

Mix buffer and acetonitrile in ratio of 88:12.

Diluent 1: Mix methanol and Glacial acetic acid (75:25)

Diluent 2: mix ACN and Water (90:10)

Chromatographic Conditions maintained during operation are as follow-

Column : 100 *4.6 Kromasil

Detection wavelength : 294 nm

Flow rate : 1.0 ml/ml

Injection volume : 10 µl

Run time : 15 mins

Column oven Temperature: Ambient

Table 1: Formulation table of tablets batch F1-F9

Ingredients (mg/tab)	F1	F2	F3	F4	F5	F6	F7	F8	F9
D.R.C.	250	250	250	250	250	250	250	250	250
MCC PH102	45	42	39	45	42	39	45	42	39
Colloidal silicon dioxide	10	10	10	10	10	10	10	10	10
Pearlitol SD 200	15	15	15	15	15	15	15	15	15
Sucralose	6	6	6	6	6	6	6	6	6
Crospovidone	9	12	15	-	-	-	-	-	-
SSG	-	-	-	9	12	15	-	-	-
CCS	-	-	-	-	-	-	9	12	15
Magnesium stearate	5	5	5	5	5	5	5	5	5
Mango flavour	10	10	10	10	10	10	10	10	10
Total weight	350	350	350	350	350	350	350	350	350

D.R.C.: Drug resin complex; CCS : Croscarmellose sodium; SSG : Sodium starch glycolate

Standard Solution: 100 mg of Ofloxacin was weighed and dissolved in 100 ml of diluent 1. Sonicate it for about 10 mins (1000µg/ml). Further dilute 2 ml of stock solution to 100 ml volumetric flask using diluent 2 (20µg/ml)

Sample Solution: 20 tablets of formulation were weighed accurately, the average weight was determined and then grinded it to fine powder. A quantity equivalent to 100 mg of Ofloxacin was weighed and transferred to a 100 ml volumetric flask and add 70 ml of diluent 1 and sonicate it properly for about 10 mins. Finally make up the volume to 100 ml using same diluent. Further dilute 2 ml of above solution to 100 ml volumetric flask using diluent 2. The solution was filtered through 0.45 µm filter and injected in the system.

b) Weight variation

The procedure followed for weight variation test was in accordance with Indian Pharmacopoeia 2010. Twenty tablets were selected randomly and weighed. Average weight of the tablet was determined. These tablets were weighed individually and the weight variation was determined. (Limit- > ±5%)

c) Tablet hardness

The resistance of tablets to shipping or breakage, under conditions of storage, transportation and handling before usage, depends on its hardness. The hardness of tablet of each formulation was checked by using Monsanto hardness tester. The hardness was measured in terms of kg/cm^2.

d) Friability

Friability is the measure of tablet strength. Roche friabilator was used for testing the friability using the following procedure-

Twenty tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm dropping the tablets through a distance of six inches with each revolution. After 4 mins, the tablets were weighed and the percentage loss in tablet weight was determined.

e) Thickness

Thickness of tablet is important for uniformity of tablet size. Thickness was measured using Vernier Calipers. It was determined by checking thickness of ten tablets from each batch.

f) Wetting Time

A piece of tissue paper folded twice was placed in a small Petri dish (10 cm diameter) containing 10 ml of water. A tablet was put on the tissue paper and allowed to wet completely. The time required for complete wetting of the tablet was then recorded.

g) Water Absorption Ratio

A small piece of tissue paper folded twice was placed in a small Petri dish containing 6 ml of water. A tablet was put on the paper and the time required for complete wetting was measured. The wetted tablet was then reweighed. Water absorption ratio, R was determined by using following formula given below-

$$R = 100 \times Wa - Wb / Wb$$

Where,

Wb = weight of tablet before water absorption

Wa = weight of tablet after water absorption

h) Uniformity of Dispersion

Place 2 tablet in 100 ml of water and stir gently until completely dispersed. A smooth dispersion is obtained that passes through a sieve screen with a nominal mesh aperture of 710 µm (sieve no.22).

i) In vitro Disintegration Study

This test is performed to ensure disintegration of tablets in water, if it is to be used as a dispersible tablet. To be in compliance with the Pharmacopoeial standards, dispersible tablets must disintegrate within 3 minutes when examined by the disintegration test for tablets.

j) Dissolution Testing

Tablets of each batch were subjected to dissolution rate studies. In-vitro dissolution study was carried out to determine the drug release from various formulations. The release characteristic was determined by withdrawing aliquots of sample at the interval of 10 minutes for 30 minutes.

Equipment used:

Dissolution Test Apparatus USP Type II (paddle), Electrolab TDT-08L

Details of dissolution test

Apparatus	:	Electrolab TDT-08L
Speed	:	50 rpm
Volume of medium	:	900 ml
Stirrer	:	Paddle type
Aliquot taken after 10 minute	:	5 ml
Medium used	:	0.1 N HCl
Temperature	:	37 ± 0.5°C

Stability studies

The stability studies were carried out on the optimized formulations, at 30^0C/75% RH and 40^0C/ 75% RH for a period of three months. The tablets were packed in the PVC blister packs and were placed in the accelerated stability chamber at 30^0C/75% RH and 40^0C/75% RH for a period of 3 months. Sampling was done at a predetermined time intervals of 0, 30 and 90 days. The formulation was evaluated for different physicochemical parameters viz. % assay and in-vitro release of the drug.

RESULTS AND DISCUSSION

Selection of λ_{max} of drug

The standard solution was scanned in the range of 200-400 nm and absorption maximum was found to be 294 nm.

Preparation of drug-resin (resinate) complex

The resinate was prepared by batch process, nine batches were prepared using three ion exchange resins in different concentration. Following trials were done with different ion exchange resins so as to find out the maximum drug loading efficiency with complete taste masking-

Trial with Indion 204:- Indion 204 ion exchange resin was used for the first trial in different drug: resin ratios i.e. 1:1, 1:1.5 and 1:2 to prepare drug- resin complex C1, C2 and C3 respectively. It was observed that complex C3 showed 92.35% drug loading with moderate taste masking.

Trial with Indion 214:- Same as that of Indion 204, Indion 214 was also used in three different concentrations. By using 1:1, 1:1.5 and 1:2 drug: resin ratio three complexes C4, C5 and C6 were prepared. The complex C6 showed 91.65% drug loading with complete taste masking.

Trial with Tulsion 335:- By using 1:1, 1:1.5 and 1:2 drug: resin ratio three complexes C7, C8, and C9 were prepared. It was observed that complex C8 showed 98.25% of drug loading with complete taste masking and complex C9 showed 98.32% of drug loading with complete taste masking. There was no significant difference between batch C8 and C9 with respect to the drug loading.

Selection of drug-resin ratio complex

Three ion exchange resins were used and by varying the concentration of ion exchange resin nine batches of drug-resin complex were prepared. Depending upon the taste masking and % drug loading efficiency batch C8 was selected for the formulation of tablets.

Characterization of solid drug-resin complex

A) FT-IR Study, Tulsion 335

FT-IR spectrum of Ofloxacin, tulsion 335, ofloxacin-tulsion 335 complex and formulated tablets (F9) were recorded. FTIR spectrum reveals that the Ofloxacin in the pure form as well as in the complex form with tulsion-335 showed peaks of functional group at same wavelength. Hence it was concluded that there was no interaction between Ofloxacin and tulsion 335. The FTIR spectrum of tablets (F9) also showed major peaks at the same wavelength as that of Ofloxacin.

B) DSC (Differential Scanning Calorimetry)

DSC of Ofloxacin, tulsion 335, ofloxacin-resin complex and formulated tablets (F9) were recorded (figures 1, 2, 3, 4 respectively). In DSC spectrum of Ofloxacin there was an exothermic peak at 269^0C which may be because of oxidation or recrystallization. It indicates the amorphous nature of the Ofloxacin. DSC spectrum of tulsion 335 showed an exothermic peak at 88^0 C, indicating the amorphous nature of resin. DSC spectrum of drug-resin complex showed an exothermic peak at 93^0 C which was due to tulsion 335. At the later stage two fused exothermic peak at 196^0 C and 216^0 C were observed. The shift in the exothermic peak of the drug may be due to the complex formation between the Ofloxacin and tulsion-335.At last DSC spectrum of tablets (F9) were recorded which showed an exothermic peak at 93^0 C which is due to the tulsion 335. At the later stage an exothermic peak was observed at 166 ^{0} C which may be due to the complex formation between Ofloxacin and tulsion-335and due to other excipients present in the formulation.

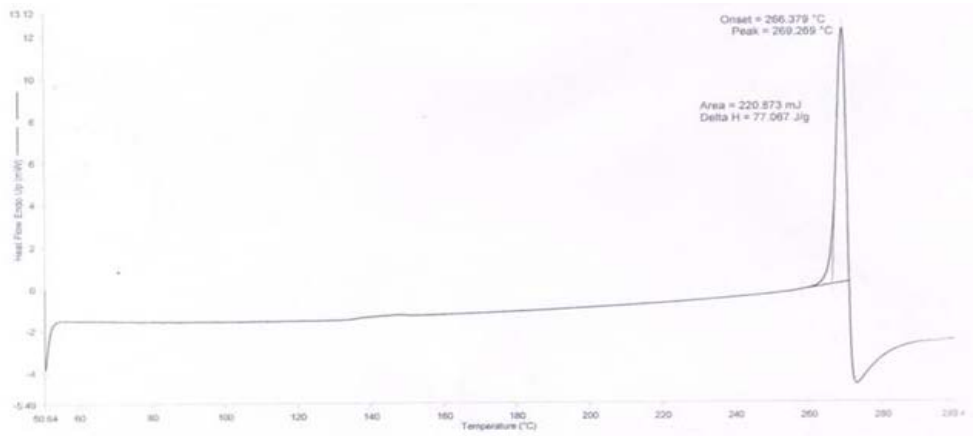

Figure 1: DSC spectrum of Ofloxacin

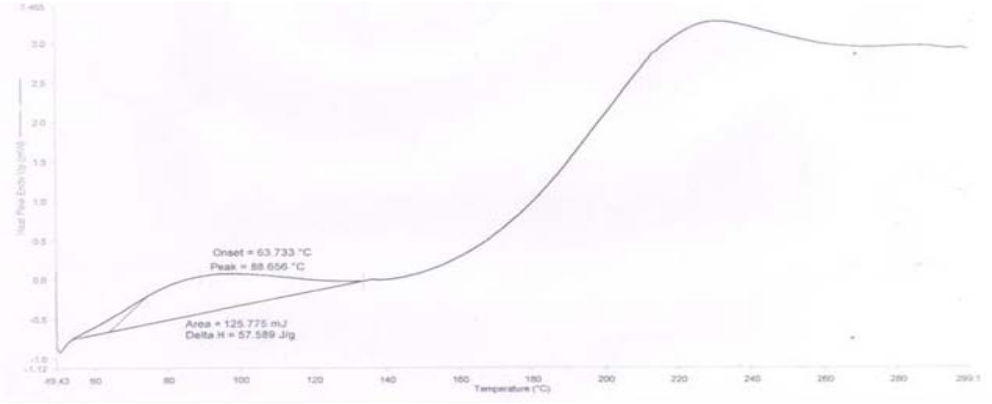

Figure 2: DSC spectrum of Tulsion 335

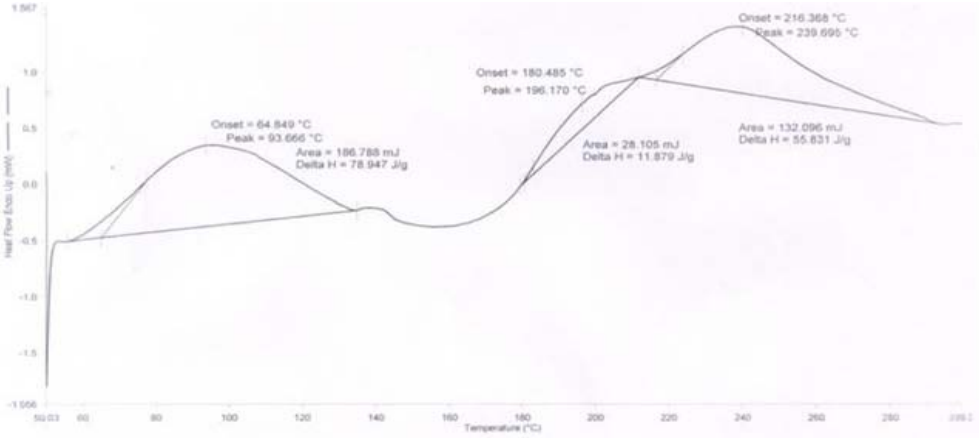

Figure 3: DSC spectrum of Ofloxacin- tulsion 335 complex

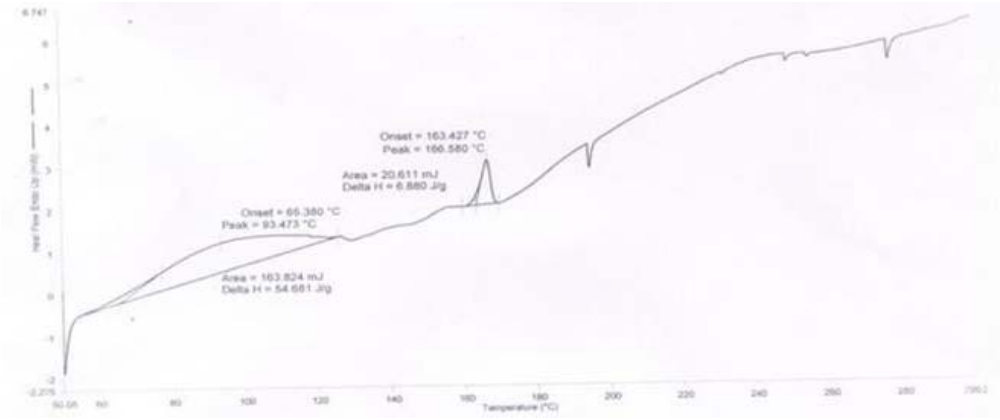

Figure 4: DSC spectrum of tablet of formulation batch F9

Table 2: Physical Characteristics of powder blend

Batch	Bulk density	Tapped density	Hausner's ratio	Angle of repose	Sieve Analysis	
					Below 40#	Above 60#
F1	0.447	0.504	1.127	27.32	61%	39%
F2	0.445	0.501	1.125	26.56	59%	41%
F3	0.453	0.515	1.136	25.21	58%	42%
F4	0.439	0.512	1.166	28.32	60%	40%
F5	0.452	0.507	1.121	26.64	65%	35%
F6	0.432	0.505	1.168	25.87	64%	36%
F7	0.451	0.535	1.186	27.89	57%	43%
F8	0.435	0.503	1.156	25.45	62%	38%
F9	0.446	0.510	1.143	26.65	60%	40%

Table 3: Evaluation of Tablets

Parameter	Formulation batch				
	F1	F2	F3	F4	F5
Hardness* (Kg/cm^2)	6.21 ±0.14	5.72 ±0.21	5.62 ±0.24	5.43 ±0.35	6.11 ± 0.33
Friability* (%)	0.35 ±0.11	0.44 ±0.21	0.46± 0.15	0.48± 0.19	0.37± 0.12
Content Uniformity* (%)	99.23±1.3	99.32±1.4	100.02±1.2	98.45±1.3	99.23±0.9
Wetting time* (sec)	40 ±1.41	38 ±1.21	35 ±1.23	41 ±1.75	37 ±1.52
Thickness* (mm)	3.7 ±0.05	3.7 ±0.07	3.65 ±0.08	3.7 ±0.05	3.6 ±0.09
Weight variation*	351±1.51	350 ±1.21	349 ±1.54	352 ±1.60	350 ±1.32
Disintegration time* (sec)	38 ±1.52	35 ±1.21	33 ±1.32	39 ±1.45	37 ±1.75
Uniformity of dispersion	+	++	++	+	++

Table 3: Evaluation of Tablets (Continued.....)

Parameter	Formulation batch			
	F6	F7	F8	F9
Hardness* (Kg/cm^2)	6.12 ± 0.28	5.91 ± 0.14	5.43 ± 0.35	6.21 ± 0.22
Friability* (%)	0.43 ± 0.11	0.56 ± 0.15	0.61 ± 0.16	0.23 ± 0.13
Content Uniformity* (%)	99.35 ± 1.54	99.41 ± 1.45	99.65 ± 1.56	99.85 ± 1.24
Wetting time* (sec)	34 ± 1.53	35 ± 1.32	29 ± 1.43	25 ± 1.75
Thickness* (mm)	3.65 ±0.08	3.65 ±0.10	3.6 ±0.09	3.7 ±0.05
Weight variation*	352 ±1.75	351±1.45	350 ±1.69	350 ±1.10
Disintegration time* (sec)	34 ±1.73	30 ±1.21	24 ±1.42	19 ±1.23
Uniformity of dispersion	++	++	+++	+++

(*Represent mean ± S.D.) (n=3); where, + = not dispersed uniformly;
++ = passable dispersion (some fragment remains); +++ = uniformly dispersed

Table 4: Dissolution Profile of formulation Batch F1-F9

Time (mins.)	% Cumulative Drug Release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
10	70.57	72.63	75.43	68.92	72.48	74.56	75.76	77.73	79.95
20	88.94	91.56	92.53	85.67	86.56	88.95	90.98	92.87	95.78
30	92.87	94.65	96.31	88.64	92.73	94.56	92.67	95.98	99.54

Evaluation of powder blend

Powder blend of each batch were evaluated for various parameter mentioned in the experimental section. Results are shown in the table 2.

Evaluation of formulated tablets

Tablets of all batches were evaluated for the various parameters. Results are shown in the table 3 and 4.

Selection of optimised batch

From the all formulated batches F1- F9 it was observed that the batch F9 which contains the croscarmellose sodium as a super disintegrant shows all physical properties viz. Friability, content uniformity, wetting time etc as satisfactory. Tablets of this batch showed lowest disintegration time and uniform dispersion when placed in small amount of water. The in-vitro release profile of the tablets showed that more than 95% release of the drug. So the formulation batch F9 was selected as optimised batch and the stability studies were carried out for this batch.

Stability Study

Tablets of batch F9 was kept for stability studies were examined. The color of the tablets was similar before and after stability studies. Surface texture of tablets packed in PVC Blister packs does not show any significant change at 30°C/75%RH and 40°C/75%RH after 3 months. This indicated that the tablets not absorb moisture from the environment.

Various others parameters were also checked after specific interval of time and found satisfactory.

CONCLUSION

The main aim of the present investigation was to mask the bitter taste of the drug by using ion exchange resin and to formulate the rapid disintegrating tablet with sufficient mechanical strength. The various ion exchange resins viz. Indion 204, 214 and Tulsion 335 were used for this purpose. Drug-resinate complex was prepared by varying the drug: resin ratio. Depending upon the taste of the complex and % drug loading the complex C8 was selected. This complex showed complete taste masking with 98.25% drug loading.

The above taste masked complex was used for formulating the rapid disintegrating tablet. The tablets were prepared by using direct compression technique with the addition of super disintegrant and directly compressible filler. Three super disintegrant viz. Cros povidone, sodium starch glycolate and croscarmellose sodium were tried in different concentration. The dry mix blend of all batches were evaluated for different derived properties viz. angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio, in order for determine the flow characteristics. All the batches show satisfactory flow ability, nine formulations (F1-F9) of drug-resinate complexes was prepared. 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 99.23-100.02 (acceptable limit) and the Hardness of the tablets was found between 5.43-6.21 kg/cm^2. Friability of tablets was found less than 1% indicating good mechanical resistance. The wetting time of tablets from batches F1 to F9 was found to be in the range of 25-41 sec. and disintegration time of all batches was found in the range of 19-39 sec.

Batch F-9 was selected as optimized batch containing croscarmellose sodium as a super disintegrants in 4.3% concentration. Batch F9 has less disintegration time of 19 sec (Avg. of 6 tablets). The dissolution study of batch F9 showed 99.54% of drug release within 30 min. The stability study of batch F9 was carried out at 30^{0}C-75% RH and 40^{0}C-75% RH. The tablets were found to be stable at such condition and other parameters were found to be unaffected. The formulation F9 was found to be best as this formulation showed adequate disintegration time, hardness and short wetting time. Out of three super disintegrants formulations, formulation containing croscarmellose sodium show best result. Finally it was concluded that rapid disintegrating taste masked tablet of Ofloxacin can be successfully prepared by direct compression technique with the help of tulsion 335 as taste masking agent and croscarmellose sodium as a disintegrant.

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