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Research Paper

FORMULATION OPTIMIZATION AND EVALUATION OF ORALLY DISINTEGRATING TABLETS OF GEMIFLOXACIN MESYLATE

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Drug delivery through oral route is widely accepted through all over world. Orally Disintegrating tablet is most suitable tablet than conventional tablet. The main characteristic which is in the favors of Orally disintegrating tablet is that there is no need of water to take it. Due to this it become more suitable dosage form for pediatric and geriatric patients. In the present work an attempt has been made to develop taste masked orally disintegrating tablet of Gemifloxacin using ion exchange resins (Kyron T314) as a taste masking agent. Different drug: resin ratios were tried to prepare taste masked complex. 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 two super disintegrants viz. cross povidone and sodium starch glycolate. Tablets of all batches were tested for various evaluation parameters. Tablets formulated with 10% Crospovidone (GIT05) showed lowest wetting time (19 sec). The % cumulative release of drug from tablet (GIT05) gave the highest dissolution (84.48 %) at the end of 120 minutes. It was thus possible to formulate orally disintegrating tablets of Gemifloxacin using simple and cost effective, Ion Exchange Resin Complexation technique.

Keywords: Gemifloxacin Mesylate, Ion Exchange Resin, Drug Resin Complex (DRC), super disintegrant.

INTRODUCTION

Children, older persons, and many other persons including disabled or incapacitated patients often have trouble swallowing tablets or capsules. In these situations, it is desirable to provide the drug either in a chewable solid form or a liquid dosage form. The undesirable taste is one of several important formulation problems that are encountered with certain drugs. Oral administration of bitter drugs with an acceptable degree of palatability is a key issue for health care providers, especially for pediatric patients. Masking of bitter taste of drugs is an important parameter for the improvement of patient compliance.[1]

One of the attractive methods for oral drug delivery systems preferably is the use of ion exchange resins as carrier. 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. 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 Resinates, directly into

solution and then absorbed in the usual way. The resin passes through the GI tract without being absorbed.[2]

Gemifloxacin Mesylate is chemically 7-[(4Z)-3-(aminomethyl) -4- (methoxyimino) pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4- dihydro-1,8-naphthyridine-3-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 Gemifloxacin with ion exchange resins and complex was further formulated into the rapid disintegrating tablet by direct compression method.

MATERIALS AND METHODS

Materials

Gemifloxacin Mesylate was obtained as a gift sample from Cipla private Laboratories Ltd. Ion exchange resins obtained from Corel Pharma Limited as a gift sample.

Preparation of standard curve of Gemifloxacin Mesylate

100 mg of Gemifloxacin Mesylate was dissolved in 0.1 N HCl in 100 ml of volumetric flask and the solution was made upto volume with 0.1 N HCl.

The standard solution of Gemifloxacin Mesylate was subsequently diluted with 0.1 N HCl to obtain a series of dilutions containing 1, 2, 3, 4 and 5 µg of Gemifloxacin Mesylate in 1 ml solution. The absorbance of these solutions was measured at 267 nm using UV-VIS spectrophotometer (ELICO, Model SL 1500) against blank.

Preparation of drug-resin complex

Drug resin complexes (DRC) were prepared by using batch process. Accurately weighed amount of Kyron T314 dispersed in a beaker containing deionized water and allowed to swell for 30 minutes. Swelled resin slurry was filtered on what man filter paper. Then it was washed with deionized water and then activated with 1 N HCl. The acid activated resin was rewashed with water until neutral pH was reached. Drug resin complex (DRC) was prepared, by placing acid activated resin in a beaker containing deionized water. Accurately weighed amount of Gemifloxacin Mesylate was

added slowly to the resin slurry and stirred for 3hours in magnetic stirrer. During stirring, pH of the drug resin slurry was measured frequently and adjusts to 6.5 by using 0.1 M KOH. After three hours of stirring, the DRC was separated from dispersion by filtration and washed with deionized water. DRC was dried at 55°C until it was dry. The dried mass was powdered and sieved through 60-mesh sieve. Complex was evaluated for drug loading efficiency.

Characterization of Complex:[8,9]

- Effect of drug-resin ratio on complex formation

Ratio of the resin to drug can greatly impact the complex formation and ultimately affects the taste masking ability. It was necessary to find out the optimum drug to resin ratio. In each case drug resin complexes (DRC) of Gemifloxacin Mesylate and Kyron T314 were prepared in 1:1, 1:2 and 1:3 ratios. The taste masking ability and drug loading efficiency were estimated.

- Drug loading efficiency for DRC

DRC equivalent to 100 mg of Gemifloxacin Mesylate was weighed accurately and was transferred into 100 ml of volumetric flask. 100 ml of 0.1 N HCl was added to this volumetric flask and was stirred continuously for 1 hour on a magnetic stirrer. After stirring, this solution was filtered through whattman filter paper. Filtered sample solution was suitably diluted with 0.1 N HCl and the amount of drug dissolved were determined by UV spectrophotometer, by measuring the absorbance of the sample at 267 nm.

- Differential Scanning Calorimetry

Differential scanning calorimetry (DSC) thermo grams of the Gemifloxacin, Kyron T314 and drug resin complexes were recorded on NETZSCH DSC 204 (Germany). Samples (2-7 mg) were sealed into aluminum pans and scanned at a heating rate of 10°C/min over a temperature range of 20-360°C under a nitrogen gas stream.

- Fourier Transform Infrared (FT-IR) studies

FT-IR spectra of Gemifloxacin, Kyron T314 and drug resin complexes were recorded in the range of 400 to 4,000 cm−1 using a Bruker alpa FTIR spectrophotometer (Bruker, Germany) by the KBr disc method.

Formulation of tablets:

Gemifloxacin Mesylate orally disintegrating tablets were prepared by direct compression method using DRC (1:3) and the superdisintegrants in different quantity. According to the formula given in Table 1, all the ingredients were passed through 40-mesh sieve separately and collected. The DRC (ratio 1:3) containing amount equivalent to 100 mg of Gemifloxacin Mesylate was mixed with the other excipients and compressed into tablets, after lubrication with magnesium stearate, and talc by using 16 station rotary tablet compression machine equipped with10 mm flat faced punches. The tablet weight was adjusted to 700 mg.

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Table 1: Formulation of ODTs of Gemifloxacin- Kyron T314 complex

Ingredients mg/tab	Formulation				
	GIT01 (mg)	GIT02 (mg)	GIT03 (mg)	GIT04 (mg)	GIT05 (mg)
DRC	481	481	481	481	481
Mannitol	78	78	63	68	59
Povidone	42	42	42	42	42
Sodium starch glycolate	51	---	33	---	---
Crospovidone	---	51	33	61	70
Aspartame	28	28	28	28	28
Menthol	6	6	6	6	6
Talc	7	7	7	7	7
Magnesium stearate	7	7	7	7	7
Total weight (mg)	**700**	**700**	**700**	**700**	**700**

Evaluations of Granules[10'11]

Granules were evaluated for Angle of Repose, bulk density, tapped density and Hausner's ratio.

Physical characterization of tablets [12,13]

- **Hardness**

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablet was determined using Monsanto hardness tester. It is expressed in kg/cm^2. Five tablets were randomly picked and hardness of the tablet was determined.

- **Weight variation test**

The weight variation test is carried out in order to ensure uniformity in the weight of tablets in a batch. Twenty tablets were randomly selected and accurately weighed, in grams on an analytical balance

- **Friability Test**

According to the BP specifications 10 tablets were randomly selected and placed in the drum of a tablet friability test apparatus (Electrolab, India). The drum was adjusted to rotate 100 times in 4 min. the tablets were removed, dedusted and accurately weighed. The percent weight loss was calculated.

- **Wetting time**

A piece of tissue paper (12 cm X 10.75 cm) folded twice was placed in a small petridish (ID = 6.5 cm) containing 6 ml of Sorenson's buffer pH 6.8. A tablet was put on the paper, and the time for complete wetting was measured. Three trials for each batch were performed and the standard deviation was also determined.

- **Water absorption ratio**

Water absorption ratio, R was determined using following equation.

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

Where,

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Wa = Weight of tablet after water absorption

Wb = Weight of tablet before water absorption.

- **Disintegration Time**

The test is carried out on the 6 tablets using the apparatus specified in IP distilled water at 37^0 C ± 2^0C was used as a disintegration media and the time in second taken for complete disinigration of the tablet with no palpable mass remaining in the apparatus was measured in seconds.

- **In vitro dissolution studies**

In vitro dissolution studies for fabricated Fast Dissolving tablet is carried out by using USP XXIV paddle method at 50 rpm in 900 ml of Sorenson's buffer pH 6.8 as dissolution media, maintained at 37±0.5^{0}C. 10 ml aliquots was withdrawn at the specified time intervals, filtered and assayed spectrophotometrically. An equal volume of fresh medium, which was prewarmed at 37^{0}C is replaced into the dissolution medium after each sampling to maintain the constant volume throughout the test. Dissolution studies are performed in triplicate.

RESULTS AND DISCUSSION

Standard Graph of Gemifloxacin Mesylate

Table 2: Standard graph of Gemifloxacin in 0.1N HCl

Concentration ((µg/ml)	Absorbance
1	0.141
2	0.272
3	0.386
4	0.527
5	0.648

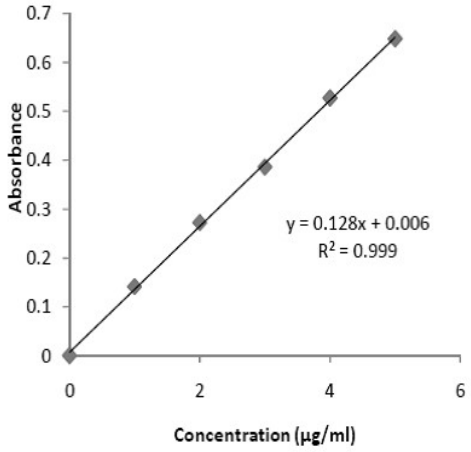

Fig. 1: Calibration curve of Gemifloxacin in 0.1 N HCl

Evaluation of Gemifloxacin- Kyron T314 Complex

- Effect of drug-resin ratio on complex formation

Table 3: Effect of Drug Resin Ratio on complex formation

Drug – Resin Ratio	Time (hrs)	Percent Gemifloxacin Loading
1:1	3	55.67
1:2		72.16
1:3		83.17

- Differential Scanning Calorimetry

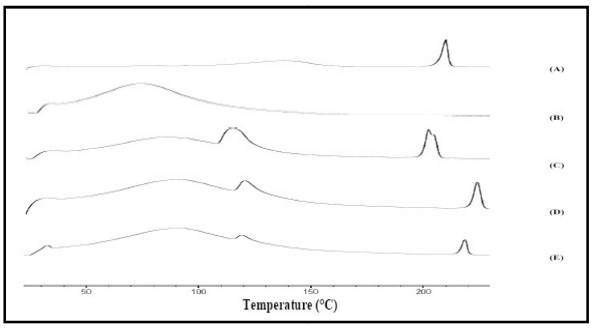

Fig. 2: DSC Thermograms of (A) Gemifloxacin (B) Kyron T314 (C) G- Kyron T314 (1:1) (D) G- Kyron T314 (1:2) (E) G- Kyron T314 (1:3)

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- Fourier Transform Infrared (FT-IR) Studies

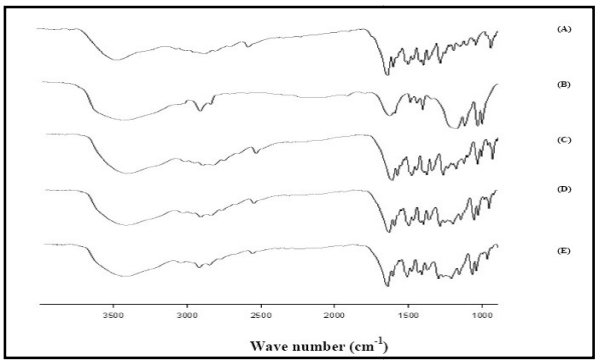

Fig. 3: FTIR Spectras of (A) Gemifloxacin (B) Kyron T314 (C) G- Kyron T314 (1:1) (D) G- Kyron T314 (1:2) (E) G- Kyron T314 (1:3)

- Drug loading efficiency for DRC

Table 4: Drug loading efficiency for DRC

Drug – Resin Ratio	Time (hrs)	Percent Gemifloxacin Loading
1:3	3	83.18

Precompression parameters of granules

Table 5: Evaluation of precompression parameters of granules (Drug + T314)

Formulation	Angle of repose (θ)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Compressibility index (%)	Hausner's ratio
GIT01	28.2	0.81	0.93	14.81	1.15
GIT02	27.8	0.82	0.93	13.41	1.13
GIT03	27.4	0.82	0.92	12.20	1.12
GIT04	28.7	0.82	0.93	13.41	1.13
GIT05	28.3	0.83	0.93	12.05	1.12

Post-compression parameters of Gemifloxacin ODTs

Table 6: Evaluation of Post-compression parameters of Tablets (Drug + T314)

Formulation	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Weight Variation (mg)	Drug content (%)	Disintegration Time (sec)	Wetting time (sec)	Water Absortion ratio
GIT01	5.38	4.2	0.18	1.8	86.15	80	63	0.35
GIT02	5.38	4.2	0.19	1.3	84.04	73	62	0.36
GIT03	5.36	4.3	0.18	1.5	85.41	40	33	0.38
GIT04	5.37	4.2	0.21	1.4	85.11	33	28	0.39
GIT05	5.38	4.1	0.22	1.4	86.47	22	19	0.41

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Table 7: *In vitro* dissolution studies of Gemifloxacin ODTs (Drug + T314)

Time (min)	Cumulative % of drug release				
	GIT01	GIT02	GIT03	GIT04	GIT05
5	30.56	35.24	39.27	40.63	42.64
10	34.38	41.86	43.90	44.93	46.48
15	38.22	48.85	49.72	53.38	54.23
20	43.68	54.61	55.21	56.15	58.05
25	47.12	56.45	58.96	61.71	62.25
30	52.94	59.04	62.04	64.42	65.77
45	57.28	64.62	67.20	69.73	70.29
60	64.37	69.82	72.54	72.94	75.17
90	70.62	75.63	78.46	79.18	81.04
120	77.12	80.21	82.37	83.85	84.48

The percentage drug content of all the tablets was found to be between 84.04 and 86.47 %. The results of in vitro disintegration of all the tablets were found to be within the prescribed limits and satisfying the criteria of fast dissolving tablets. The lowest wetting time (19 sec) was obtained with formulation GIT05. Among all the formulations GIT05 which contain 10% of Crospovidone gave the highest dissolution (84.48 %) at the end of 120 minutes.

CONCLUSION

Gemifloxacin Mesylate is a broad spectrum antibiotics, active against both Gram-positive and Gram negative bacteria. This drug is highly bitter in taste. The present investigation was undertaken with an overall objective of studying the drug resin complexation (DRC) to mask the bitter taste of the drug. The resin, namely, Kyron T314 was selected for the study of feasibility of employing drug resin complexation for masking the bitter taste of drug. The main objectives of this research project were to study the drug resin of these drug resin complexes.

From the present study, it is concluded that the Kyron T314 can be used for taste masking and for formulating slow release products.

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