Formulation and In-vitro Evaluation of Gemifloxacine Orodispersible Tablet

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Abstract

Gemifloxacin is a fluoroquinolone antibacterial with actions and uses similar to those of ciprofloxacin. It is granted orally, as the mesylate, for the treatment of community acquired pneumonia and acute bacterial exacerbations of chronic bronchitis .Various super disintegrants were used in this study including croscarmellose sodium, sodium starch glycolate and crospovidone. The formulas were measured for flow properties, tablet hardness, friability, content uniformity, wetting time, *in vitro* disintegration time (DT), and drug release profiles. Crospovidone (CP) showed the shortest DT (*p<0.05*) among other superdisintegrants and fast drug release. The disintegration time of the gemifloxacin orodispersible tablet was decreased to a significant level upon addition of glycine (disintegration enhancer).

It is worthwhile to mention that the addition of chitin (porosity enhancer) has a dramatic effect on the disintegration time of the prepared gemifloxacin orodispersible tablet. The formula containing 15% of CP and 8% of chitin (GF15) had the shortest DT (24.6sec.), superior drug release profile [the time required for 80% of the drug to be released (t80%) and percent drug released in 2 min (D2min) were 6.1 min. And 55.3% respectively] so it was selected as the best formula. The drug-excipient compatibility study indicated that no interaction of the drug occurred with the components of the formula, and the accelerated stability study showed no significant changes (*p<0.05*) in tablet properties. The overall results suggested that the prepared formula of gemifloxacin (GF15) could be utilized as a new dosage form for the oral administration.

Key Words: Gemifloxacin, orodispersible, disintegration, direct compression

Introduction

The aim of these new technologies (Orodispersible tablets) is the generation of fast dissolving tablets with improved hardness, taste, stability, dose capacity, easier manufacturing process and cost.

Orodispersible Tablets

Among the dosage form developed for the case of medication is the orodispersible tablet. United States Food and Drug Administration (FDA) defined Orodispersible tablets (ODT) as “A solid dosage form containing medicinal substance or active ingredient which disintegrates rapidly usually within a matter of seconds when put on the tongue. Orodispersible tablets are also known as an orally disintegrating tablet, mouth-dissolving tablets, melt-in mouth tablets, fast dissolving tablets, rapimelts, porous tablets, quick dissolving tablet[1]. European pharmacopeia adapted the term Orodispersible tablet as “A dosage form that is to be placed in the mouth where it disperses rapidly before swallowing.ODT products have been developed for numerous indications ranging from migraines, for which rapid onset of action is important) to mental illness for which patient compliance is important for treating chronic indications such as depression and schizophrenia [2]. The concept of ODT emerged with an objective to improve patient’s compliance. These dosage forms rapidly disintegrate and/or dissolve to release the drug as soon as they come in contact with saliva, thus obviating the need for water during administration and make the taking of medication easy, an attribute that makes ODT highly attractive for pediatric and geriatric patients. Difficulty of swallowing conventional tablets and capsules is common among all age groups, especially in elderly and dysphasic patients [3].

Advantages of Orodispersible tablets [4]

Orodispersible tablet offer all the advantages of solids along with liquids oral dosage forms, besides exclusive beneficial properties that mentioned below:-

1. ODT represent a suitable dosage form to overcome the swallowing problem that associated with the conventional oral solid dosage form especially in the elderly, institutionalized psychiatric patients, multiple sclerosis and cerebral palsy patients, stroke victims, type-2 diabetes, Parkinson's disease and other neurological disorders.

2. Orodispersible tablets are expandable dosage form when the site of pharmacological action of the active drug is the mouth such as local anesthetic for tooth aches, oral ulcers, cold sores, or teething.

3. Improvement the safety of drugs by eliminating the risk of suffocation during oral administration of conventional formulations due to physical obstruction, which is beneficial for travelling patient who does not have access to water.

4. Their pleasant mouth feel property helps to change the perception of medication as bitter pill particularly in pediatric patients.

5. Rapid disintegration of tablets may result in a quick dissolution and rapid absorption which provide a rapid onset of action.

Disadvantages of Orodispersible tablets [5]

Although the useful properties of the ODT that mentioned above, it has some disadvantages which are notably their high friability and low physical resistance, which causes manipulation problems not only during their processing but also with patients. Also patients who concurrently take anti-cholinergic medications, patients who suffer from Sjögren's syndrome or dryness of the mouth due to decreased saliva production may not be able to take ODT formulations.

Unsuitable drug characteristic for ODTs[6]

1. Short half-life and frequent dosing.

2. Very bitter or otherwise unacceptable taste because taste masking cannot be achieved.

3. Required controlled or sustained release.

Excipients commonly used for ODTs preparation [7]

The fundamental properties of the tablets are fast absorption or wetting of water into the tablets and disintegration of associated particles into individual components for fast dissolution. This requires that excipients should have high wettability, and the tablet structure also should have a highly porous network. Because the strength of the tablet is related to compression pressure, and porosity is inversely related to compression pressure, it is important to find the porosity that allows water absorption faster in maintenance of higher mechanical strength. Mainly seen excipients in ODT are reproduced below; at least one disintegrant, diluents, a lubricant, and optionally a swelling agent, sweeteners, and flavoring agents.

1. Ideal bulk excipients for orally disintegrating dosage forms should have the following properties:
2. 1. Disperses and dissolves in the mouth within a few seconds without leaving residue.
3. 2. Masks the drug's offensive taste and offers a pleasant mouth feel.
4. 3. Enables sufficient drug loading and remains relatively unaffected by changes in humidity or temperature.

Types of superdisintegrants

There are mainly three types of superdisintegrants:

1. Crospovidone (CP) it's also called on kollidon CL and polyplasdone XL. It's a cross- linked homopolymer of N-vinyl- Pyrrolidone. CP is a water insoluble tablet disintegrant and dissolution agent used in which the major mechanism of disintegration is wicking.CP is well suited for orodispersible tablets because it has better compressibility compared with other superdisintegrants, high capillary activity, smooth mouth feel, rapid disintegration, harder, less friable tablet pronounced hydration capacity, and little tendency to form gels. Moreover, the rate and extent of liquid uptake and swelling of CP is not reduced in 0.1 N hydrochloric acid as when compared with aqueous medium [8].

2. Croscarmellose Sodium (CCS)

It's also called Ac-Di-Sol and solute. It's a cross-linked polymer of sodium carboxymethylcellulose. The cross-linking serves to reduce water solubility, allowing the material to swell and absorb many times its weight of water. Ac-Di-Sol is used as superdisintegrant for tablets prepared by direct compression or wet granulation, and for capsules [9].

3. Sodium Starch Glycolate (SSG)

It also called explotab and primojel. It's made from cross-linking sodium carboxymethylstarch. SSG is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations. Disintegration occurs by rapid uptake of water followed by a rapid and enormous swelling [10].

Table 1 the types of superdisintegrnet

Superdisintegrants	Example	Mechanism Of action	Special comment
Crosscarmellose Ac-Di-Sol Nymce ZSX PrimelloseSolutab Vivasol L-HPC	Cross linked cellulose	-Swells 4-8 folds in < 10 seconds. -Swelling and wicking both.	-Swells in two dimensions. -Direct compression or granulation -Starch free
Crosspovidone Crospovidone M Kollidon Polyplasdone	Cross linked PVP	-Swells very little And returns to original size after compression but act by capillary action	-Water insoluble and spongy in nature so get porous tablet
Sodium starch glycolate Explotab Primogel	Cross linked starch	-Swells 7-12 folds in < 30 seconds	-Swells in three dimensions and high level serve as sustain release matrix
Alginic acid NF Satialgine	Cross linked alginic acid	-Rapid swelling in aqueous medium or wicking action	-Promote disintegration in both dry or wet granulation
Soy polysaccharides Emcosoy	Natural super disintegrant	-Does not contain any Starch or sugar. Used in nutritional products	

Technologies Used for Preparation of Orodispersible Tablets

Different technologies are used for manufacturing of orodispersible tablets, ranging from classic methods such as direct compression to newer one like floss method. Not only unique in procedure, these methods give rise to a substantial difference in tablet characteristics such as mechanical resistance, disintegration time and dissolution rate. Ideally, although these technologies meet the special requirements for orodispersible tablets to some extent, none of them has all the desired [11].

1-Freeze Drying or Lyophilization Method

Freeze drying consists in which water is sublimed from the product after it is frozen. This technique creates an amorphous porous structure that can dissolve rapidly. The freeze-drying technique has demonstrated improved absorption and increase in bioavailability. Cisapride monohydrate (Propulsid®) and Risperidone (prepared by Janssen Pharma) are examples of drugs prepared by lyophilization [12].

2-Floss Method (Cotton candy process)

The cotton candy process is also called the candy floss process. It is named so as it utilizes a unique spinning mechanism to produce a floss-like matrix of polysaccharides or saccharides having crystalline structure, which mimic cotton candy. The matrix formed is partially recrystallized to have improved flow properties and compressibility. This candy floss matrix is then milled and blended with active ingredients and excipients and subsequently compressed to orodispersible tablet. Tramadol HCl (Relivia Flash dose/ Fuisz Technology Ltd.) is an example of a marketed drug prepared by this method [13].

3-Spray Drying:

The formulations contained hydrolyzed and unhydrolyzed gelatin as a supporting agent for the matrix, mannitol as a bulking agent and sodium starch glycolate, croscaramellose as a disintegrant. Disintegration and dissolution were further enhanced by adding an acid (e.g. citric acid) or an alkali (e.g., sodium bicarbonate). The suspension of above excipients was spray dried to yield a porous powder which was compressed into tablets. Tablets manufactured by this method disintegrated in < 20 seconds in an aqueous medium.

4-Molding Method

In this method, molded tablets are prepared by using water soluble ingredients so that the tablets dissolve completely and rapidly. The powder blend is moistened with a hydro alcoholic solvent and is molded into tablets under pressure lower than that used in conventional tablet compression. The solvent is subsequently removed by air drying. Molded tablets are very less compact than compressed tablets; they possess porous structure that enhances dissolution. Example of drug prepared by molding method is ibuprofen (Cibalgina DueFast / Eurand International) [14].

5-Direct Compression Method

Direct compression is the most applicable technology to produce orodispersible tablets. Simplicity, cost effective, less equipment and time that needed, long term stability and fewer dissolution problems(due to elimination of heat and moisture) all of these are factors stand behind direct compression preference[15].

Patented Technologies for Orally Disintegrating Drug Delivery System

The aim of these new technologies is the generation of orodispersible tablets with improved hardness, taste, stability, dose capacity, easier manufacturing process and cost. The followings are some of the patented technologies for preparation of orodispersible tablets [16].

1. Zydis Technology

Zydis was first marketed technology and introduced by Scherer Corporation (Cardinal Health, Inc.) in 1986. Zydis tablet is produced by lyophilizing the drug in a matrix usually consisting of gelatin. The product is very lightweight and fragile and must be dispensed in a special blister pack. Loratidine (Claritin Reditab/ Scherer Corporation) is an example of a marketed drug prepared by this technology.

2. Wow tab Technology

Wow tab technology was developed by Yamanouchi Pharma Technologies. 'Wow' means 'without water'. The active ingredients may constitute up to 50% w/w of the tablet. Here, saccharides of both low and high moldability are used to prepare the granules. Moldability is the capacity of a compound to be compressed. Highly moldable substance has high compressibility and thus slow dissolve ion.

3. Durasolv Technology

DuraSolv is Cima's second-generation fast-dissolving/ disintegrating tablet formulation (Cima Labs, Inc.). DuraSolv technology is best suited for formulations including relatively small doses of the active compound. Tablets made by this technology consist of a drug, fillers and a lubricant and prepared by using conventional tablets equipment and have good rigidity. These can be placed into conventional packaging system like blisters. Due to the higher force of compaction used, tablets prepared are rigid. Hyoscyamine sulfate (NuLev®) and zolmitriptan (Zolmig ZMT®)

4. Orasolv Technology

Orasolv is Cima's first orally disintegrating dosage form. It is based on direct compression of an effervescent agent and tastes masked drug. The use of effervescence causes a tablet to disintegrate rapidly in less than one minute on contact with water or saliva leaving coated drug powder. This technique is often used to develop over the counter formulations.

MATERIALS AND METHODS

Gemifloxacin

Empirical formula: $C_{18}H_{20}FN_5O_4 \cdot CH_4O_3S$

Molecular weight: 485.49

Chemical name:

(R, S)-7-[(4Z)-3-(aminomethyl)-4-(methoxyimino)-1-pyrrolidinyl]-1 cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-1, 8-naphthyridine-3-carboxylic acid.

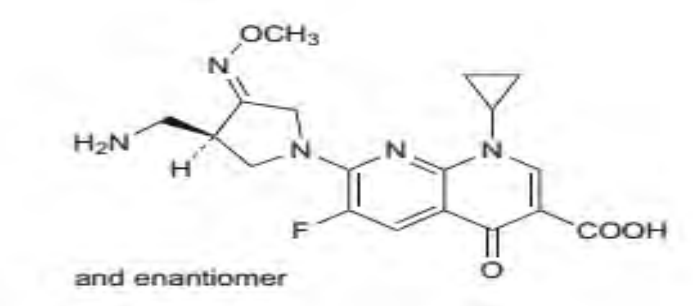

Fig. 1: Structural formula of Gemifloxacin

The mesylate salt is a white to light brown solid. Gemifloxacin is freely soluble at neutral pH (350 μg/mL at 37 ºC, pH 7.0). Melting point: 214.57 ºC

Gemifloxacin is a fluoroquinolone antibacterial with actions and uses similar to those of ciprofloxacin. It is given orally, as the mesilate, for the treatment of community acquired pneumonia and acute bacterial exacerbations of chronic bronchitis [17].

Methods

Characterization ofGemifloxacin

1-Determination of Melting Point

The melting point of GEM powder was 214.5˚C which agrees with the range that is reported in B.P. 214.5C The result indicates the purity of the drug powder.

2-Determination of λ max

Solution of GEM in Distilled water was scanned by a UV spectrophotometer from 400 to 200nm, and the λ max was determined.

Characterization of Superdisintegrants

1. Determination of swelling Index

The swelling capacity (swelling index) of the tested superdisintegrants including CP, CCS, SSG, was determined. One gram of each super disintegrant was placed in a dry cylinder fixed in a water bath at (37 C). Acidic solution (0.1 N HCl) or phosphate buffer (pH 6.5) was added gradually to these dry samples separately with continuous stirring until the volume was completed to 100 ml. The samples were incubated at 37oC for 3 hours. The volume of each superdisintegrant was calculated before the addition of the medium and at the end of the incubation time.

The swelling capacity was calculated using this equation

Swelling Capacity = $Vt - Vi/Vi \times 100$

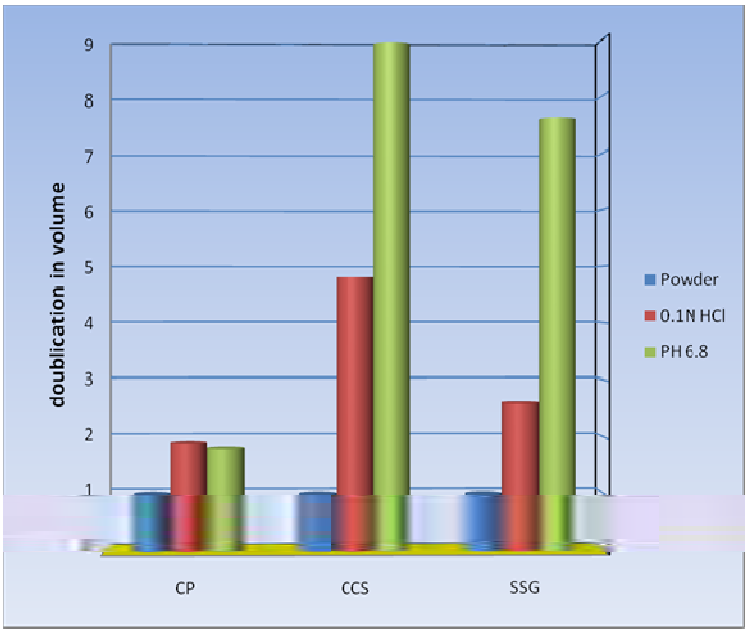

Fig. 2: Swelling capacity of crospovidone, croscarmellose sodium and sodium starch glycolate in phosphate buffer media pH 6.5 and in 0.1NHCL at 37 ± 0.5 ˚C.

Formulation of GEM Orodispersible Tablets:

Table 2 shows all formulas were prepared by direct compression method as follows:

In this method accurately weighed quantities of the active ingredient(Gemifloxacin) and the calculated excipients (except Mg stearate and talc) are mixed for 10 min using mortar and pestle after which the remaining materials were added and blended for another 2 min. Final mixtures which are compressed at about 37 KN using a single punch tablet machine.

Table 2: Different formulas of Gemifloxacin [A]

Formulation code (mg)	GF1	GF2	GF3	GF4	GF5	GF6	GF7	GF8
GEM	325	325	325	325	325	325	325	325
CP	25 (5% w/w)	50 (10% w/w)	75 (15% w/w)					
SCC				25 (5% w/w)	50 (10% w/w)	75 (15% w/w)		
SSG							25 (5% w/w)	50 (10% w/w)
Glycine								
Chitin								
saccharine	5	5	5	5	5	5	5	5
Talc	3	3	3	3	3	3	3	3
Mg stearate	2	2	2	2	2	2	2	2
Mannitol Q.S. to	500	500	500	500	500	500	500	500

Table 2: Different formulas of Gemifloxacin [B]

Formulation code (mg)	GF9	GF10	GF11	GF12	GF13	GF14	GF15
GEM	325	325	325	325	325	325	325
CP		100 (20% w/w)	75 (15% w/w)	75 (15% w/w)	75 (15% w/w)	75 (15% w/w)	75 (15% w/w)
CCS							
SSG	75 (15% w/w)						
Glycine			(4% w/w)	(8% w/w)	(12% w/w)		
Chitin						(4 % w/w)	(8 % w/w)
saccharin	5	5	5	5	5	5	5
Talc	3	3	3	3	3	3	3
Mg stearate	2	2	2	2	2	2	2
Mannitol Q.S.	500	500	500	500	500	500	500

Selecting of the Optimum Formula

In the manufacturing of ODTs, the main parameter is the disintegration time, literatures considered that 1 minute is the upper limit time, it is preferable to be less than 40 sec. or more better less than 30sec.,the rapid disintegrating tablet often associated with poor mechanical strength that mean, needing a special packaging procedure which consequently is costly.To ensure an acceptable content range of active pharmaceutical ingredient, designing of a formula being a real good flow properties was needed. These ideal characteristics may not be included in one formula. So balancing between these criteria is applicable in the decision of selecting a favorable pharmaceutical pattern.

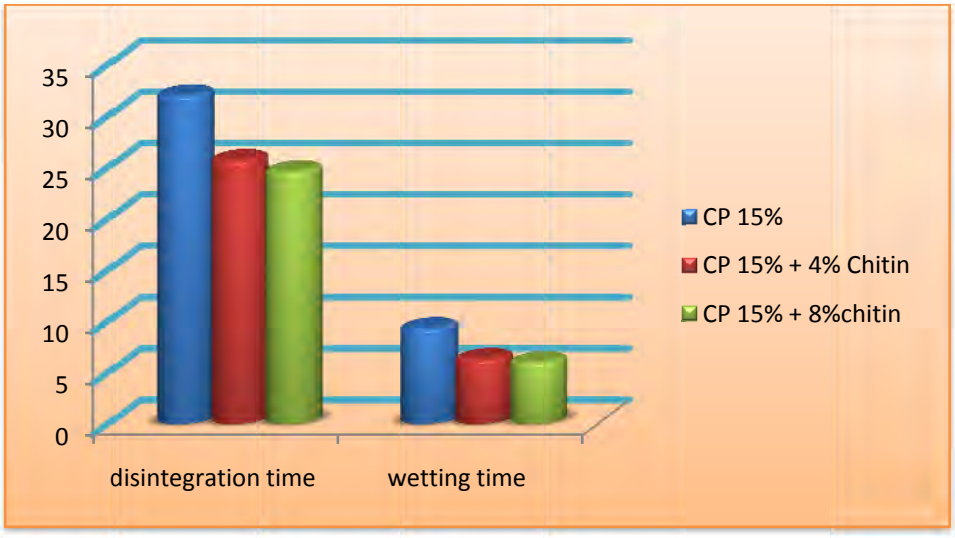

Fig. 3: Effect of addition of chitin (4 and 8 %) on the mouth disintegration time and wetting time of the prepared orodispersible tablets

From tables above along with the previous discussion, it declares a fact that formulas (GF12, GF14 and GF15) have a less disintegration time and a pharmaceutical acceptable feature and further study required to put a point on the word.

Weight variation

The results of weight variation test for the selected formulas (GF12, GF14 and GF15) showed mean value of (499.85mg ±2.18) which lies within the accepted range according to B.P which is ±5 % deviation from the average weight that is (503 – 498.06 mg)that indicate uniform tablet weights.

***In vitro* dissolution studies**

In vitro dissolution studies, as they are important for conventional tablets, also are important for ODTs since faster disintegration typically not meant rapid therapeutic onset.

In vitro drug release studies of the optimized formulations were carried out at pH 7, which selected to assess any pre-gastric absorption that may take place when some of the particles from the orodispersible formulation get lodged into the denture and gradually may get absorbed through buccal mucosa .The dissolution apparatus (USP Apparatus Type II) is rotated at 50 r.p.m since it is claimed that ODTs have a rapid disintegration rate which may lead to rapid dissolution rate which consequently may produce unclear dissolution profile.

The time required for 80% of the drug to be released (t80%) and percent drug released in 2 minutes (D2min) was included for comparing the dissolution results. As showed in figure (4) there is significant difference *P<0.05* in the release profiles between the selected formula containing the superdisintegrant (CP) (i.e.GF12GF14 and GF15) and conventional Gemfloxacin tablet active.

Table (3) declares that the t80% of GF15 has a value larger than the GF 12, GF14and conventional tablet, also GF15 have the favorable D2min (55.3%) value.

The enhanced drug release profiles for the best formulas (GF12, GF14 and GF15) is not only related to the decrement of disintegration time, but rather to the selected super disintegrant (crospovidone), Since crospovidone is a nonionic disintegrant, so no any possible ionic interaction occurs between it and the drug.

Table 3: *In vitro* dissolution parameters in distilled water (pH 7)

Formula no.	t80% (min)	D2 min (%)
GF12	9.2	41.2
GF14	9.7	43.7
GF15	6.1	55.3
Factive ®	7.9	38.4

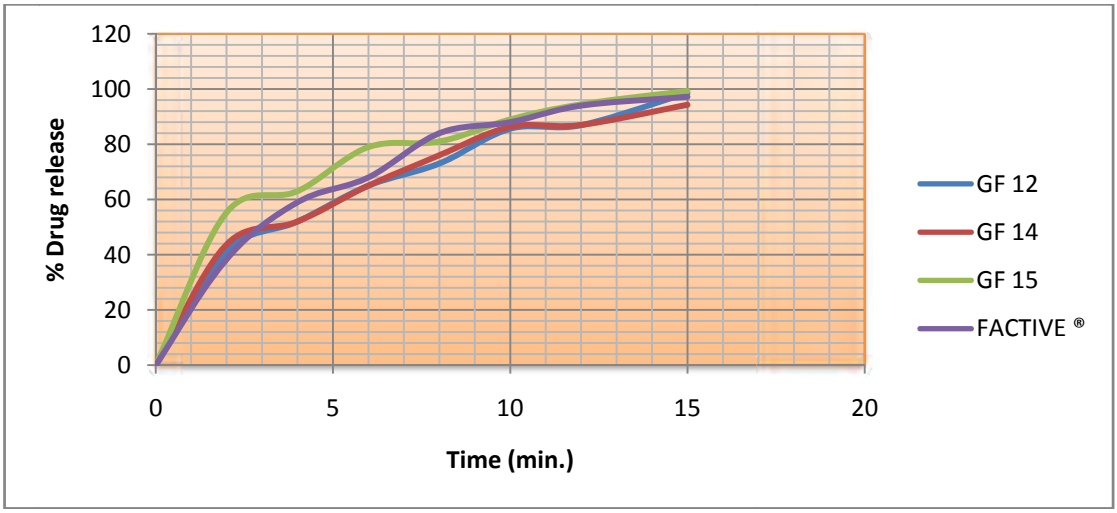

Fig. 4: Dissolution rate in PH 7

Conclusion and Discussion

Based on the results, we can conclude the following facts:

Crospovidone is the best superdisintegrant among croscarmellose sodium; sodium starch glycolate. It was the best thing in terms of showing the fastest in vitro disintegration time. Disintegration time was decreased with increasing concentration of crospovidone but further increasing will lead to decreasing the time of disintegration. Upon addition of chitin, the disintegration time is decreased significantly. Formula GF15 (crospovidone 15% + 8% chitin) have the shortest disintegration time, appropriate physical properties and a good release profile as compared with the other formulas, so it is selected as the best formula.

The overall results of this study show the possibility of utilizing the selected best formula (GF15) in the preparation of Gemifloxacin ODTs as a new dosage form for the oral administration.

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