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RESEARCH ARTICLE

Formulation and *In Vitro* Evaluation Mirtazapine Oral Disintegrating Tablets by Sublimation Method

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ABSTRACT

For the past one decade, there has been an enhanced demand for more patient friendly and compliant dosage forms. As a result, the demand for developing new technologies has been increasing annually. Since the development cost of a new drug molecule is very high, efforts are now being made by pharmaceutical companies to focus on the development of new drug dosage forms for existing drugs with improved safety and efficacy together with reduced dosing frequency, and the production of more cost-effective dosage forms. For most therapeutic agents used to produce systemic effects, the oral route still represents the preferred way of administration, due to its several advantages and high patient compliance compared to many other routes. Mirtazapine is a tetracyclic piperazino-azepine antidepressant agent that was initially approved for the treatment of major depressive disorder in the Netherlands in 1994. Drug and excipient compatibility was confirmed by comparing spectra of Fourier transform infrared analysis of pure drug with that of various excipients used in the formulation. The results of the drug-excipient compatibility studies revealed that there was no chemical interaction between the pure drug and excipients.

Keywords: Mirtazapine, tablets, sublimation method

INTRODUCTION

For the past one decade, there has been an enhanced demand for more patient friendly and compliant dosage forms. As a result, the demand for developing new technologies has been increasing annually.[1]

Since the development cost of a new drug molecule is very high, efforts are now being made by pharmaceutical companies to focus on the development of new drug dosage forms for existing drugs with improved safety and efficacy together with reduced dosing frequency, and the production of more cost-effective dosage forms. For most therapeutic agents used to produce systemic effects, the oral route still represents the preferred way of administration, due to its several advantages and high patient compliance compared to many other routes.[2]

Tablets and hard gelatin capsules constitute a major portion of drug delivery systems that are currently available. However, many patient groups such as the elderly, children, and patients who are mentally retarded, uncooperative, nauseated, or on reduced liquid intake/diets have difficulties swallowing these dosage forms. Those who are traveling or have little access to water are similarly affected.[3] To fulfill these medical needs, pharmaceutical technologists have developed a novel oral dosage form known as orally disintegrating tablets (ODTs) which disintegrate rapidly in saliva, usually in a matter of seconds, without the need to take it water. Drug dissolution and absorption as well as onset of clinical effect and drug bioavailability may be significantly greater than those observed from conventional dosage forms.[4,5] Although chewable

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tablets have been on the market for some time, they are not the same as the new ODTs. Patients for whom chewing is difficult or painful can use these new tablets easily. ODTs can be used easily in children who have lost their primary teeth but do not have full use of their permanent teeth.[6,7]

ODTs technology, which makes the tablets dissolve or disintegrate in the oral cavity without any additional water intake, has drawn a great deal of attention. ODTs are a solid dosage form that provides the rapid disintegration or dissolution of solid to present as suspension or solution form even when placed in the mouth under limited biofluid.[2,8] ODTs are known by various names such as oral dispersible tablets, quick disintegrating tablets, fast disintegrating tablets, fast or rapid dissolving tablets, porous tablets, mouth dissolving tablets, and rapimelts. The excipients used in ODT technology are usually hydrophilic in nature and can be selected on the basis of drug's physicochemical properties such as hydrophilicity or hydrophobicity. If the active pharmaceutical ingredient is hydrophobic in nature, then dosage form is called disintegrating tablet whereas, if it is hydrophilic, then the dosage form is called fast dissolving tablet. The ODT formulation defined by the Food and Drug Administration (FDA) as "a solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds when placed on the tongue." The U.S. FDA approved Zydis, ODT formulation of Claritin (loratadine) in December 1996. It was followed by a Zydis ODT formulation of Klonopin (clonazepam) in December 1997, and a Zydis ODT formulation of Maxalt (rizatriptan) in June 1998. Further, a number of drugs have been approved by regulatory authorities for ODT formulations. The aim of this article is to review the advantages, limitations, formulation challenges, manufacturing techniques, patented technologies, marketed formulations, and evaluation tests of ODTs.[2,8-19]

Drug Profile

Mirtazapine

Description

Mirtazapine is a tetracyclic piperazino-azepine antidepressant agent that was initially approved for the treatment of major depressive disorder (MDD) in the Netherlands in 1994.

This drug was first manufactured by Organon Inc. and received FDA approval in 1997 for the treatment of MDD. The effects of this drug may be observed as early as 1 week after beginning therapy.

In addition to its beneficial effects in depression, mirtazapine has been reported to be efficacious in the off-label management of various other conditions. It may improve the symptoms of neurological disorders, reverse weight loss caused by medical conditions, improve sleep, and prevent nausea and vomiting after surgery.

Excipient Profile

Sodium starch glycolate

Synonyms: Carboxymethyl starch, sodium salt; Explosol; Glycolys.

Chemical Name and CAS Registry Number: Sodium carboxymethyl starch [9063-38-1].

Applications in Pharmaceutical Formulation or Technology

It is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations [Figure 1]. It is commonly used in tablets prepared by either direct compression or wet granulation processes [Figure 2]. The usual concentration employed in a formulation is between 2% and 8%, with the optimum concentration about 4%, although in many cases, 2% is sufficient

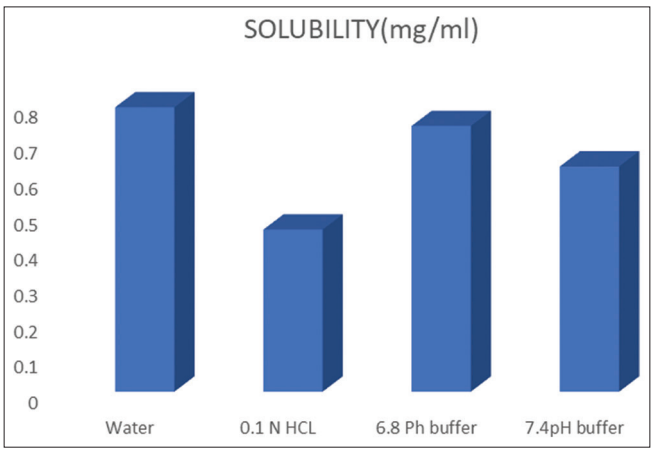

Figure 1: Solubility of mirtazapine

[Figure 3]. Disintegration occurs by rapid uptake of water followed by rapid and enormous swelling. Although the effectiveness of many disintegrants is affected by the presence of hydrophobic excipients such as lubricants, the disintegrant efficiency of sodium starch glycolate is unimpaired. Increasing the tablet compression pressure also appears to have no effect on disintegration time. Sodium starch glycolate has also been investigated for use as a suspending vehicle.

Table 1: Materials used

S. No.	Materials	Company
1.	Mirtazapine	Spectrum Labs; Hyderabad.
2.	Sodium starch glycolate	Signet Chemical Corp., Mumbai
3.	Croscarmellose sodium	Signet Chemical Corp., Mumbai
4.	Crospovidone	Signet Chemical Corp., Mumbai
5.	Aspartame	Signet Chemical Corp., Mumbai
6	Microcrystalline cellulose	Aurobindo Pharma Ltd.; Hyderabad.
7.	Talc	S.D. Fine Chem. Ltd.; Chennai.
9	Magnesium stearate	S.D. Fine Chem. Ltd.; Chennai.

Description

Sodium starch glycolate is a white to off-white, odorless, tasteless, free-flowing powder. The PhEur 2005 states that it consists of oval or spherical granules, 30–100 μm in diameter, with some less spherical granules ranging from 10 to 35 μm in diameter [Tables 1 and 2].[20-34]

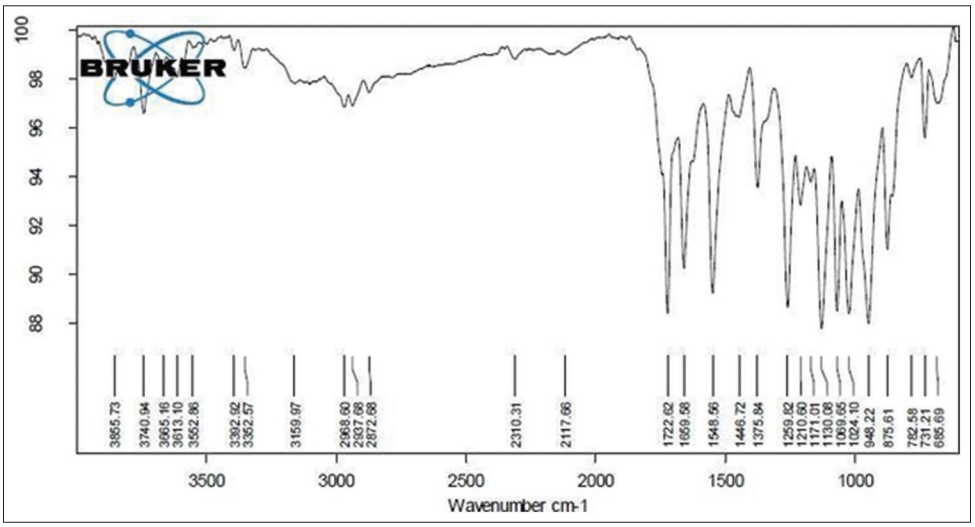

Figure 2: Infrared spectrum of mirtazapine

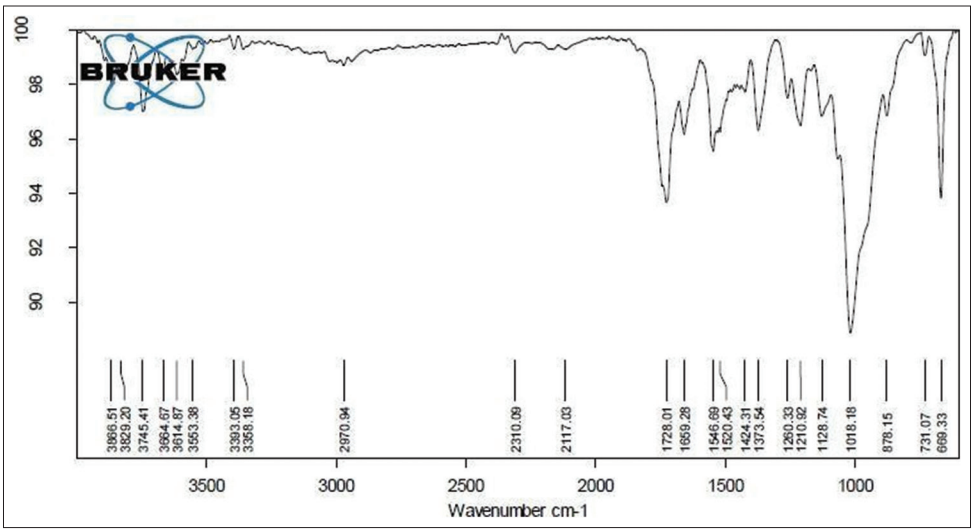

Figure 3: Infrared **spectrum of mirtazapine and excipients**

Table 2: Instruments and equipment used

S. No.	Instruments/Equipment	Company
1.	Digital balance	Essae-Teraoka Ltd., DS-852j
2.	Hardness tester	Monsanto
3.	Friability test apparatus	Electro lab USP EF2
4.	Hydraulic press	Clit pilot press
5.	Vernier caliper	Pico India Ltd.
6.	Tablet dissolution tester (USPII)	Lab India DS8000
7.	Tap density tester	K.E. India
8.	UV spectrophotometer	PG Instruments, T60
9.	FT-IR spectrophotometer	Shimadzu-8400 S
10.	pH meter	Hanna Instruments.

RESULTS AND DISCUSSION

Solubility Studies

Solubility of mirtazapine was carried out at 25°C using 0.1 N HCl, 6.8 phosphate buffer, 7.4 pH buffer, and purified water.[35,36]

Medium	Solubility (mg/ml)
Water	0.793
0.1 N HCl	0.452
6.8 pH buffer	0.741
7.4 pH buffer	0.628

Drug Excipient Compatibility

Drug and excipient compatibility was confirmed by comparing spectra of Fourier transform infrared analysis of pure drug with that of various excipients used in the formulation.

DISCUSSION

Form the drug excipient compatibility studies, we observe that there are no interactions between the pure drug (mirtazapine) and optimized formulation (Mirtazapine + Excipients) which indicates that there are no physical changes.

SUMMARY AND CONCLUSION

- The present study is an attempt to select the best possible disintegrant – subliming combination to formulate oral disintegrating tablets of mirtazapine, which disintegrates in matter of seconds in the oral cavity, thereby reducing the time of onset of pharmacological action.
- SSG and CCS were used as disintegrants. In all the formulations, magnesium stearate and talc were used as lubricant and glidant, respectively.
- The results of the drug-excipient compatibility studies revealed that there was no chemical interaction between the pure drug and excipients.
- Sublimation method was employed to formulate the tablets, because of its cost-effectiveness and due to reduced number of manufacturing steps.
- The pre-compression parameters such as bulk density, tapped density, Carr's index, and angle of repose were determined. All the formulations showed acceptable flow properties.
- The post-compression parameters such as the hardness, thickness, friability and weight variation, disintegration time, disintegration time in oral cavity, and *in vitro* release were carried out and the values were found to be within IP limits.
- The percentage drug content of all the tablets was found to be between 82.24 and 98.16% of mirtazapine, which was within the acceptable limits.
- Among all the formulations, F9 shows 99.13% drug release at the end of 20 min. F9 contains camphor (30 mg), it shows better % drug release when compared to other formulations.
- Hence, F9 was considered as the optimized formulation.
- The drug release kinetics shows that the optimized formulation F9 follows first-order drug release.

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