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MCC SANAQ® burst: A unique carrier for formulation of sublingual tablets

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Abstract: The major impediment that affects formulation of rapidly disintegrating sublingual tablet (RDSTs) is the compromise between instantaneous disintegration and sufficient physico-mechanical properties of active pharmaceutical ingredient and excipients. The present study deciphers about evaluation of the influence of selected diluents on the characteristics of RDSTs manufactured using novel ready-to-use excipient MCC SANAQ® burst by direct compression. The rapidly disintegrating characteristics of three different grades of Avicel and new MCC SANAQ® burst were investigated. All the prepared formulations (F1-F14), using various grades of MCC were examined for their bulk density, tapped density and porosity. The formulations were further tested for weight variation, content uniformity, friability, wetting time, disintegration and dissolution. Studies reveled that Formulation F1, containing MCC SANAQ® burst as a diluent was found to provide quick disintegration in 0.25 ± 0.14 sec and had short wetting time of 0.45± 1.16 sec, as compared to formulations that were prepared by using other grades of Avicel. The results revealed that MCC SANAQ® burst is a promising excipient to prepare RDSTs.
Key words: MCC SANAQ® burst, sublingual tablet, Avicel grades, direct compression, Duloxetine HCl.

Introduction

Regardless of outstanding advancement in drug delivery system, the oral route of drug administration is the most conspicuous method of administration of drug for achieving systemic effect[1]. Rapidly-disintegrating sublingual tablets (RDSTs) have edge far beyond the use of accustomed dosage forms with novel approaches those are emerging continuously day by day.

Buccal and sublingual routes are generally endorsed as routes of drug delivery through oral mucosa. Sublingual delivery involves placement of the dosage form beneath the tongue, this route is used to provoke quicker onset of action, whereas buccal route is used to produce sustained action[2]. The sublingual route usually produces a faster onset of action than that of orally administered tablets and the part absorbed through the sublingual blood vessels bypasses the hepatic first-passmetabolic processes[3, 4].

Various approaches have been reported in past to formulate sublingual tablets. The most conventional preparation methods are moulding, lyophilisation, direct compression, sublimation, mass extrusion and spray drying[5].

Among all the aforementioned technique, direct compression method is a well-accepted manufacturing process due to improved product yield with reduction in manufacturing cost[6].

The selection of proper type, grade, and proportion of excipients is critically important in tablet formulations manufactured by direct compression. This is especially desirable in case of diluents, which constitute the largest proportion of the powder matrix used in tablet preparation[7]. A successful RDSTs tablet formulation should have rapid disintegration with acceptable weight variation, content uniformity, sufficient hardness and minimal friability to withstand manufacturing, shipping, and handling.

Non-active ingredients for RDSTs have to be selected based on material characteristics and desired functionalities likedefined bulk density, porosity, particle size distribution, good flowability, enhanced compaction and quicker disintegration[8].

Generally, microcrystalline cellulose (MCC) has good compressibility, imparting strength and higher dilution potential. It is one of the most commonly used as a diluent in direct compression for tablet preparation[9, 10]. In this present work, three standard marketed grades (Avicel PH-101, Avicel PH-102, and Avicel PH-301) were compared with newly developed MCC SANAQ® burst on tableting properties of RDSTs manufactured using direct compression method.

In the present study, Duloxetine HCl (DXH) has been used a model. It is manufactured by Eli Lily researchers, has gained approval from U.S. Food and Drug Administration (FDA) for treatment of major depressive disorders. It has also been approved for the treatment of diabetic neuropathy in September 2004 by U.S.FDA[11, 12]. The major challenge associated with the oral delivery of DXH is its solubility and gastric degradation. It is a BCS class II drug and is acid labile[13]. In order to overcome the drug degradation from the stomach, an approach was made to formulate RDSTs of duloxetine HCl for systemic delivery by using different grades of MCC.

The manufacturing of RDSTs using MCC SANAQ® burst has not been reported in literature. In the present study, the influence of diluents' physical properties on characteristic of prepared RDSTs was examined. Sublingual tablets were prepared using various grades of Avicel and MCC SANAQ® burst. All prepared formulations were evaluated for surface morphology, thickness, hardness, friability, disintegration time, and dissolution characteristics.

Materials and Methods

Materials

Duloxetine HCL was gifted by Abbot Pharmaceuticals, Ahmedabad, India. MCC (Avicel PH-101; Avicel PH-102; Avicel PH-301) was gifted by Signet Chemical Private Limited, Mumbai, India. MCC SANAQ® burst; Low-substituted hydroxyl propyl cellulose (LH-11) and Mannitol (Pearlitol-SD 200) were procured from Arihant Trading Company, Mumbai, India. Magnesium stearate and Aerosil-200 were got from Loba Chemie Pvt. Ltd., Mumbai, India.

Measurement of physical properties of diluent

Using tap density analyzer (Electrolab ETD-1020, Mumbai, India) with 50 cm^3 volume cylinder, bulk density and tap density of MCC grades (MCC SANAQ® burst , Avicel PH-101, 102, 301) were measured and porosity of excipients was also calculated. All the procedures were repeated three times for each diluent.

Preparation of Rapidly-disintegrating sublingual tablets of Duloxetine HCl

Active pharmaceutical ingredient (Duloxetine HCl) and other inactive ingredients were weighed in required quantity as mentioned in **Table I**. Ingredients were mixed in geometric dilution after screening through sieve no.52. The tablets were compressed by using 6.5 mm die (Rotary punch machine, trover pharmatech, India). In all the formulation mentioned in **Table I**, ratio of MCC: L-HPC (9:1) was constant to get optimum disintegration time[4,14, 15]. Duloxetine HCl complex powder equivalent to 22 mg of duloxetine HCl was taken in all the formulations (F1 to F4). Magnesium stearate and Aerosil-200 were maintained 0.75% w/w and ratio of mannitol (Pearlitol-SD) was kept constant at 15% to provide tensile strength[16].

Table 1 Composition of Duloxetine HCl RDSTs. Tablet weight was kept constant at 150 mg.

Ingredients (mg)	Formulation Code			
	F1	**F2**	**F3**	**F4**
Drug-Complex	42	42	42	42
MCC (SANAQ® burst)	75.6	--	--	--
MCC (Avicel pH 301)	--	75.6	--	--
MCC (Avicel pH 101)	--	--	75.6	--
MCC (Avicel pH 102)	--	--	--	75.6
Mannitol (Pearlitol® SD200)	22.5	22.5	22.5	22.5
L-HPC (LH 11)	8.4	8.4	8.4	8.4
Magnesium Stearate	0.75	0.75	0.75	0.75
Aerosil 200	0.75	0.75	0.75	0.75

Determination of various properties of tablet

Tablet thickness, diameter, surface area and volume of tablet

Tablet thickness and diameter were measured by using digital vernier caliper (Naugra Export, Ambala, India). This parameter can help to calculate the tablet surface area and volume of tablet by using the following equations (1) and (2), respectively

$$A = 2\pi r^2 + 2\pi rh \quad (1)$$

$$V = \pi r^2 h \quad (2)$$

Where A is the surface area of tablet; V, volume of tablet; h, thickness of tablet and r is the radius of tablet.

Weight variation, Hardness, Friability, Drug content study

Weight variation test had been performed according to US pharmacopoeial guidelines. Randomly, 20 tablets were selected from every batch. Individual tablet was weighed by using analytical balance (Shimadzu AX 200, Japan). Average weight with standard deviation was noted.

Hardness of the tablets was measured by Monsanto hardness tester. Friability of tablet was performed by using friabilator (Friabilator FT-1020, Lab India, India). Preweighed sample of tablet was put in the friabilator, and rotated for 100 revolutions. After completion of revolution, tablets were made dust free, and reweighed. According to guidelines, friability should not more than 1%.

Drug content uniformity was determined by dissolving the crushed tablets in pH 6.8 phosphate buffer and filtered through 0.45 µm PTFE filter.Samples were diluted and analyzed at 289 nm by using UV spectrophotometer (Shimadzu 1800, Japan).

Wetting time (WT) and Water Absorption Ratio (WAR)

Wetting time and water absorption ratio was determined, which simulates the action of saliva in contact with tablet. Diametrically folded whatman filter paper was kept in a petri dish (6.5 cm in diameter) containing 6 ml of simulated saliva. Weighed tablet was kept on the paper containing amaranth powder on the upper surface of tablet. The time required for the formation of pink color was measured as wetting time[17]. Wetted tablet was removed and reweighed to determine water absorption ratio by using equation **3**.

$$WAR = W_a - W_b / W_b \quad (3)$$

Where, W_a and W_b are the tablet weights after and before wetting.

Disintegration test

Disintegration test was performed by using disintegration apparatus (Lab India DT-1000, India) with using pH 6.8 buffer as media at 37± 0.5°C. All the studies were repeated six times and the mean data was recorded.

Dissolution test

Dissolution test was done by using eight assembly dissolution chamber (Lab India DS-8000, India). Dissolution of formulation had been performed by USP apparatus II (paddle type) at 37±0.5° C with 50 rpm in 900 ml pH 6.8 phosphate buffer. Samples were collected from time to time in specific time interval. Same volume was replaced with fresh pH 6.8 buffer which was previously maintained at same temperature to maintain sink condition. The withdrawn samples were analyzed spectrophotometrically at 289 nm[18]. The calibration curve of Duloxetine HCl was made in pH 6.8 phosphate buffer. It was found to linear from 10-60µg/ml (regression ≥ 0.99).

Result and Discussion

Physical properties of diluents

It was observed that, the porosity of MCC SANAQ® burst found to be higher amongst all other MCC grades; this indicates it has higher void volume. This was further confirmed by its lower bulk density and tapped density **(see Table 2).** On the other hand, there was no much more significant difference observed in physico-mechanicalproperties of Avicel PH-101, PH-102 and PH-301 grades.

It has been reported that MCC SANAQ® burst is the different polymorphic type of Avicel PH-102. From Table 2, values shows that MCC SANAQ® burst has lower true density value. Many factors can influence cellulose powder density and its properties. These factors vary between the types of cellulose polymorphism characters[19].

Table 2 Physical properties of various grades of microcrystalline cellulose (n=3)

Grades	Bulk density (mean± S.D.)	Tapped density (mean± S.D.)	% Porosity (mean± S.D.)
SANAQ® burst	0.26± 0.003	0.37±0.031	30.51±1.74
Avicel PH 301	0.40± 0.016	0.52±0.007	23.22±0.14
Avicel PH 101	0.33± 0.002	0.44±0.005	24.44±0.96
Avicel PH 102	0.34± 0.005	0.44±0.014	23.18±1.32

S.D. =Standard Deviation.

Thickness, diameter, surface area and volume

Tablet of all the formulations irrespective to the grade of microcrystalline cellulose had diameter (6.49 ± 0.02mm); thickness (4.39±0.17mm); surface area (155 mm^2) and volume (145.15 mm^3).

Hardness, Friability, Weight variation, Drug content

According to USP guidelines, all the batches passedthe weight variation test as well as friability test. All the Avicel grades (F2 to F4) exhibited lowest friability compared to F1 batch. This result caters that tablets containing Avicel PH101, PH 102 and PH 301 have superior interparticulate bonding than MCC SANAQ® burst **(see Table 3)**.It can be taken into account that the difference in interparticulate bonding between MCC SANAQ® burst and Avicel grades is due to the difference in their polymorphism. It means MCC Avicel grades have better compaction properties than MCC SANAQ® burst. This thing was further confirmed by low hardness found in case of MCC SANAQ® burst at same compression force.

Disintegration time of tablet is the most vital parameter which needs to be optimized during the development of sublingual tablets. According to USP disintegration test for sublingual tablets, the disintegration apparatus for oral tablets is used without the covering plastic disks, and 2 min is specified as the acceptable time

limit for sublingual tablet disintegration (USP 31). In this study, all the batches except F1 didn't meet the desired disintegration time **(see Table 3)**. The rapid and desired disintegration of F1 formulation can be explained with the following reasons.

Mechanism of rapid disintegration by the excipients of crystalline cellulose and L-HPC is affected mainly by tablet porosity, hydrophilicity, swelling ability and inter particle force[20]. The optimized ratio of MCC: L-HPC (9:1) was exploited promising in quick disintegration in case of MCC SANAQ® burst (**from Table 2**). Because, it has higher porosity amongst other standard Avicel grades. The increase in porosity affects the capillary networks inside the tablet, this impacts rapid passage of water into tablet resulting in the instantaneous ruptures of the hydrogen bonds[21].

Table 3 Various physicochemical parameters of F1 to F4 batches

Formulation	Average Weight (mg) (mean ± S.D.) (n=20)	Hardness (n=3)	Friability (mean ± S.D.) (n=3)	Drug content (mean ± S.D.) (n=3)	Disintegration time (min) ± S.D. (n=6)
F1	148.25±0.97	3.5	0.65±0.06	97.55±1.88	0.25±0.14
F2	152.5±1.29	4.5	0.31±0.08	94.89±2.32	6.5±1.5
F3	149.25±1.06	4.5	0.36±0.18	96.22±4.86	7.36±1.33
F4	150.25±1.71	4.5	0.30±0.07	94.65±3.14	7.55±0.90

S.D. =Standard Deviation.

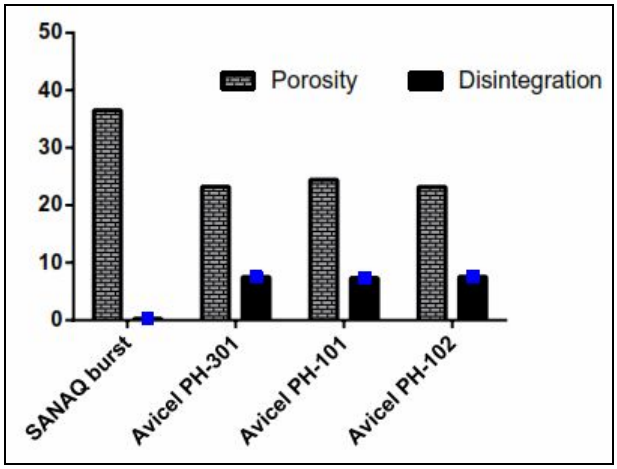

Fig. 1. Relation between porosity and disintegration

Wetting time (WT) and water absorption ratio (WAR)

The wetting time for MCC SANAQ® burst containing F1 batch was found to be remarkably lower (1 min 40 sec) than standard Avicel grades (F2 to F4) mentioned in **Table 4**. It may be due to the higher hygroscopic properties, indicating that it has higher water uptake capacity than standard Avicel grades, which can provide greater tendency to break hydrogen bonding among particles due to hydrostatic pressure inside the tablet. This phenomenon is known as wicking, which is mainly responsible mechanism for disintegration by MCC grades. Therefore, we are able to confirm that incorporating MCC SANAQ® burst into RDSTs can provide quick disintegration than other Avicel PH-101, PH-102 and Avicel PH-301 grades.

Table 4 Wetting time and water absorption ratio

Formulation	Wetting time (min) (mean± S.D.) (n=3)	Water Absorption Ratio (WAR) (mean ± S.D.) (n=3)
F1	0.45± 1.16	0.73±0.85
F2	8.02 ± 0.73	0.55±1.07
F3	7.32 ± 0.94	0.60± 1.31
F4	7.24 ± 1.63	0.49±1.55

S.D. =Standard Deviation

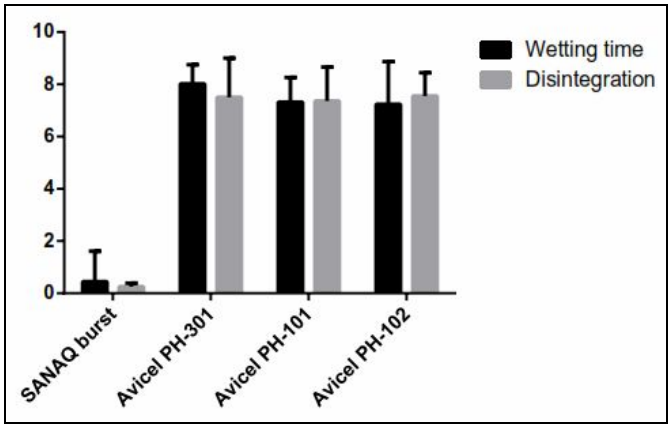

Fig. 2. Correlation between wetting time and disintegration

In vitro dissolution studies

According to the literature, the amount of drug dissolved from sublingual tablets must exceed 80% in 15 min[22]. Therefore, the resulted dissolution profile met the above mentioned requirement. Dissolution profile of formulation F1 to F4 is shown in **Fig. 1.** F1 containing MCC SANAQ® burst exhibit a robust and quick dissolution rate due to its quicker disintegration and wetting ability, whereas formulations (F2 to F4) shows the steady dissolution profile due to its longer wetting time and longer disintegration time.

Table 5 In vitro dissolution profile

Time Interval (min)	Cumulative % drug release ± S.D. (n=6)			
	F1	F2	F3	F4
2	67.30±1.86	14.96±7.87	17.60±7.05	15.40±3.11
4	79.11±3.95	28.53±6.67	35.14±8.95	25.75±5.20
6	84.83±4.80	39.24±5.05	49.42±5.27	36.88±4.19
8	88.82±3.58	53.10±8.61	59.36±6.96	53.22±6.29
10	90.48±4.01	73.33±5.33	69.81±2.22	65.98±3.21
15	94.34±1.75	87.67±2.25	90.71±4.31	86.67±4.26
20	96.61±2.18	93.86±4.13	95.32±2.67	92.90±2.83

S.D. =Standard Deviation

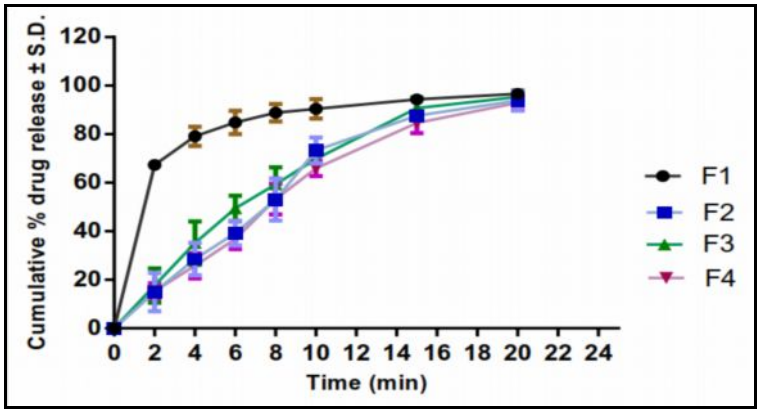

Fig.3.Cumulative %drug release (F1 to F4)

4. Conclusion

The selection of proper diluents in the process of formulating RDSTs by direct compression is critically important. The results from this study suggest that disintegration of RDSTs is dependent on the nature of diluent. We demonstrated that properties of diluents such as porosity, bulk density and tapped density are playingvital role in formulating RDSTs by direct compression. The most effective diluent in RDSTs manufactured using new ready-to-use excipient MCC SANAQ® burst which able to obtain quick disintegration with good mechanical strength, which confirms as an attractive multifunctional excipient.

Abbreviation: L-HPC (low-substituted hydroxyl propyl cellulose), MCC-Microcrystalline cellulose, RDSTs-Rapidly disintegrating sublingual tablets.

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