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EFFECT OF CO-PROCESS EXCIPIENTS IN FORMULATION OF ODTs USING A MODEL DRUG

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Keywords:

Co-processed excipients, Water soluble drug, Poor water-soluble drug, Oral disintegrated the tablet

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ABSTRACT: Different types of excipients were compared, in terms of their effect in (oral disintegrated tablets-ODTs) to optimize drug delivery and manufacturability. Therefore, the influence of excipients on the quality of ODTs was investigated by formulating and evaluate ODTs using an equal dose of water-soluble Baclofen (B) and poorly water-soluble Meloxicam (M) as model drugs. ODTs of both drugs were prepared using nine different co-process excipients for (B1-B9) and (M1-M9) formula (Pharmaburst®, Ludiflash®, F-melt®, Prosolv HD 90®, Prosolv SMCC 5O®, Prosolv ODT G2®, ProsolvEASYtab SP®, ProsolvEASYtab Nutra®, Lactose microfine), respectively by direct compression method. The prepared ODTs were evaluated for their: drug content, weight variation, thickness, disintegration time, wetting time, hardness, friability, and *in-vitro* dissolution. Both B-ODTs and M-ODTs showed no significant difference in the results of ODTs evaluation, by Using Design Expert 10 to select the best formulae of both drugs the best formulae were for poor water-soluble M9 (Lactose) > M3 (F-melt) > M6 (pro ODT) > M1 (Ph.brust) and for water-soluble: B4(Pro HD 90) > B3 (F-melt) > B6 (Pro ODT) > B1 (Ph.brust) F-melt®, Prosolv ODT G2®, and Pharmaburst®500 co-processed excipients showed the best result of quality control test and performed with no significant difference between water soluble and poor water-soluble drug, made them highly recommended to be utilized in ODT formulation.

INTRODUCTION: Orodispersible drug delivery system is a novel drug delivery system that aims to improve the safety and efficacy of drug molecule as well as to achieve better patient compliance.

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Its significance can be shown as administration without water, the accuracy of dosage, easy palatability, an alternative to liquid dosage forms, ideal for pediatric and geriatric patients and quick onset of action. Thus, with these tablets, disintegration time is greatly decreased and is rapidly dispersed or dissolved releasing the drug instantaneously [1].

According to the Pharmacopoeial definition, orodispersible tablets consist of uncoated tablets designated to be placed in the mouth where they

disintegrate rapidly in the saliva. The *in-vitro* disintegration time should not be longer than 3 min. This kind of tablets can be taken without any liquid [2]. The center for drug evaluation and research, US food and drug administration defined ODT as A solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a part of seconds, when placed upon the tongue [3]. In recent, excipients are the massive components of any pharmaceutical formulation. Excipients have been appropriately assessed for safety and are included in a drug delivery system to support the processing of the drug delivery system within its production, enhance stability, bioavailability, patient acceptability or enhance any other attributes [4]. Directly compressible co-processed excipient: The excipient which has widely been an extension of the food industry, it has taken up the novel use of particle engineering and material sciences.

The co-processing is the most largely explored method for the preparation of directly compressible adjuvants because it is cost effective and can be prepared in-house based on the functionality needed [5]. Among co-processed excipient systems, Pharmaburst®, Ludiflash®, F-melt®, Prosolv HD 90®, Prosolv SMCC 5O®, Prosolv ODT G2®, ProsolvEASYtab SP®, ProsolvEASYtab Nutra®, and Lactochem® microfine F-melt® is a spray-dried excipient used in orally disintegrating tablets that contain saccharides, disintegrating agent, and inorganic excipient. F-melt displays excellent tableting attribute and simplifies rapid water-penetration for a fast disintegration time [6]. The main merit Pharmaburst® is highly compatible, rapid disintegration and cost-effective. The quantity of Pharmaburst® required in a formulation will depend on the type of activity and the quantity per tablet [7].

Ludiflash® is a co-processed excipient that is used for the preparation of orally disintegrating tablets by direct compression. Typically, Ludiflash® tablets possessed high mechanical stability, a good mouthfeel and instant drug release due to fast disintegration competency [8]. On the other hand, the co-processed cellulose-based excipients are multi-functional products that, maintain the feature of MCC mixed with the functional qualities that provide the additional components to the cellulose [9]. The aim of the present work was to evaluate the application of these new co-processed excipient system to form orodispersible tablets by direct compression. Where two principle active ingredients (APIs) of different solubility were chosen as models for this study.

MATERIALS AND METHODS:

Materials:

- Baclofen was a kind gift from Misr Company for Pharmaceutical Industries (Cairo, Egypt).
- Meloxicam was obtained as a gift sample from Amoun Pharmaceutical Company (Cairo, Egypt).
- Pharmaburst®500 was a gift from SPI Pharma (Wilmington, DE, USA).
- Ludiflash® was provided by BASF (Ludwigshafen, Germany).
- Prosolv ODT G2®, Prosolv HD 90®, Prosolv SMCC 50®, ProsolvEASYtab SP®, Prosolv EASYtab Nutra were a gift from JRS Pharma GmbH & Co., KG (Rosenberg, Germany).
- F-melt® Type C was a gift from Fuji Chemical Industry Ltd. (Toyama-Pref, Japan).
- Lactochem ® Microfine (Lactose microfine) was a gift sample from (Borculo Domo, Netherlands).

Methods:

Evaluation of Flow Properties of Powder:

Bulk and Tapped Densities: Powder was poured gently through a glass funnel into a graduated cylinder cut exactly to 10 ml mark. The excess powder was removed using a spatula, and the weight of the cylinder with pellets required for filling the cylinder volume was calculated. The cylinder was then tapped from a height of 2.0 cm until the time when there was no more decrease in the volume. Bulk density (ρb) and tapped density (ρt) were calculated [10].

$$\text{Tapped density } (\rho t) = \text{Weight of sample} / \text{Tapped volume}$$

$$\text{Bulk density } (\rho b) = \text{Weight of sample} / \text{Bulk volume}$$

Compressibility Index and Hausner Ratio: Carr's index and Hausner ratio. Carr's index (Carr 1965) and hausner ratio (Hausner 1967) for powders were calculated from bulk and tapped densities [11]. Carr's compressibility index and the Hausner ratio to provide a measure of the flow properties and compressibility of powders.

Hausner's quotient (ratio) = Tapped density / Bulk density

Carr's compressibility = (Tapped density - Bulk density) / Tapped density × 100

Preparation of Oral Disintegrated Tablets:

Preparation of Oral Disintegrated Tablets of Baclofen (B): Direct compression method was used to prepare Fast disintegrating tablets containing 10 mg of Baclofen [12]. The drug and the directly compressible excipients were mixed by adding a small portion of each at a time and blend it to get a uniform mixture and compressed into tablets of 70 mg single punch tablet machine (Royal Artist, India) 6 mm **Table 1**.

TABLE 1: COMPOSITION OF DIFFERENT ODTS PREPARED BY DIRECT COMPRESSION USING DIFFERENT CO-PROCESSED EXCIPIENTS WITH WATER-SOLUBLE DRUG

Ingredients (mg) Formulae	B1	B2	B3	B4	B5	B6	B7	B8	B9
Baclofen	10	10	10	10	10	10	10	10	10
Pharmaburst®	60								
Ludiflash®		60							
f-melt®			60						
Prosolv HD 90®				60					
Prosolv SMCC 5O®					60				
Prosolv ODT G2®						60			
ProsolvEASYtab SP®							60		
ProsolvEASYtabNutra®								60	
Lactose microfine									60
Total (mg)	70	70	70	70	70	70	70	70	70

Preparation of Oral Disintegrated Tablets of Meloxicam (M): The accurately weighed amounts of ingredients were mixed as shown in **Table 2**, and directly compressed as into 70 mg tablets using single punch machine of 6 mm flat punch [13].

TABLE 2: COMPOSITION OF DIFFERENT ODTS PREPARED BY DIRECT COMPRESSION USING DIFFERENT CO-PROCESSED EXCIPIENTS WITH POOR WATER-SOLUBLE DRUG

Ingredients (mg) Formulae	B1	B2	B3	B4	B5	B6	B7	B8	B9
Meloxicam	10	10	10	10	10	10	10	10	10
Pharmaburst®	60								
Ludiflash®		60							
f-melt®			60						
Prosolv HD 90®				60					
Prosolv SMCC 5O®					60				
Prosolv ODT G2®						60			
ProsolvEASYtab SP®							60		
ProsolvEASYtab Nutra®								60	
Lactose microfine									60
Total (mg)	70	70	70	70	70	70	70	70	70

Evaluation of Prepared Tablets:

Weight Variation: Twenty tablets were selected randomly from each batch, and their average weight was determined. Then each tablet was taken individually, and its weight was calculated. That individual weight was compared with average weight [14], and the standard deviation (SD) was calculated.

Thickness Variation: The thickness of ODTs from each formulation was measured with a micrometer (BDM Co., Germany) [15] then the mean thickness and SD were calculated.

Friability Test: It is measured by mechanical strength of tablets. Friabilator (Copley scientific, FR 1000; Nottingham, NG42JY, UK).was used to detect the friability by the following procedure. A pre-weighed tablet was placed in the friabilator. Friabilator consists of a plastic-chamber that revolves at 25 rpm, dropping those tablets at a distance of 6 inches with each revolution.

The tablets then were rotated in the friabilator for at least 4 min. At the end of test, tablets were dusted and reweighed, the loss in the weight of the tablet is the measure of friability and is expressed in percentage as following equation [16].

% Friability = (Loss in weight / Initial weight) × 100

Hardness Test: By hardness test could be determined crushing tolerance of tablets, which is the force required to break a tablet by compression in the radial direction, hardness was measured using a tablet hardness tester Monsanto tablet hardness tester (Copley scientific, TH3/500, Nottingham, NG42JY, UK) [17] and the mean and SD values were calculated.

Drug Content: Ten tablets from each formula were assayed individually for drug content uniformity. The drug in ODTs was assayed by dissolving each tablet in simulated saliva fluid (pH = 6.8). The solution was then filtered, properly diluted, and the absorbance was spectrophotometrically measured at λ_{max} = 363 nm and 266 nm for (M) and (B) correspondingly. Each tablet contents must be between 85-115% of the average content [18].

Wetting Time (WT): The wetting time can be measured by using circular tissue papers of 10 cm in diameter, which are placed in a Petri dish of 10 cm diameter. Ten milliliters of water-soluble dye like eosin solution is added to the Petri dish.

A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach the upper surface of the tablet is noted as the wetting time [19]. Any value of more than 3 min was considered a slow WT. The WT for each formulation was carried out in triplicate, and the results were expressed as mean ± SD.

***In-vitro* Disintegration Time (DT):** Tablet was added to 10 ml of phosphate buffer solution, pH 6.8 at 37 ± 0.5 °C. The time required for complete dispersion of a tablet was measured [20]. *In-vitro* disintegration time (DT) for each formulation was determined in triplicate, and the results were expressed as mean ± SD.

***In-vitro* Dissolution:**

For (M) Tablets: *In-vitro* dissolution tests were performed with dissolution apparatus (Vision® Classic 6TM, Hanson Research, USA), set with a paddle speed of 100 rpm using 500 ml of pH 6.8 phosphate buffer at 37 ± 0.5 as a dissolution medium [21]. At specified time intervals (1, 2, 3, 4, 5, 6, 8, 10, 15, 20, 25, 30) min aliquot of 5 ml of dissolution media were withdrawn and replaced with an equal volume of the fresh medium drug content was assayed spectrophotometrically at 363 nm, drug concentration was expressed as cumulative percent drug dissolved [22]. *In-vitro* dissolution for each formulation was performed in triplicate, and the results were expressed as mean ± SD.

For (B) Tablets: An *in-vitro* dissolution study was conducted using tablet dissolution test apparatus USP XXIII (Vision® Classic 6TM, Hanson Research, USA) at 100 rpm [23]. The dissolution medium consisted of 500 ml phosphate buffer pH 6.8, maintained at temperature 37 ± 0.5 ºC. Sample of 5 ml of the medium was taken and filtered and 5 ml of fresh dissolution medium was replaced24 at time intervals (1, 2, 3, 4, 5, 6, 8, 10, 15, 20, 25, 30) min and the absorbance of collected samples was measured spectrophotometrically at 266 nm, drug concentration was expressed as cumulative percent drug dissolved [25]. *In-vitro* dissolution for each formulation was carried out in triplicate, and the results were expressed as mean ± SD.

Statistical Analysis: Using Design-Expert (version 10, Stat-Ease Inc., Minneapolis, USA) to select the best formulae of both drugs (water sol and poor water sol) the best formulae were selected.

RESULTS AND DISCUSSION: Pre-formulation study of blend powder of both drugs and their excipients flowability was done. The results of flowability of Baclofen in term of Carr's index (CI) were 45 ± 0.04, and for Meloxicam was 40 ± 0.019. which indicated very poor flow properties for both drugs, while after homogenous blending of each drug powder with co-process excipients the results were ranged from (13 ± 0.021, B with pharmabrust) to (28 ± 0.021 , B with lactochem) and (13 ± 0.021, M with F-Melt) to (27 ± 0.018, M with ludiflash) in term of Carr's (CI), as shown in **Table 3**, **4**.

Nine formulae of Baclofen (B1-B9) and Meloxicam (M1-M9) were prepared by direct compression; the evaluation of prepared tablets was done. The weight of different ODTs ranged from (67.02 ± 0.04 mg, B9) to (70.26 ± 0.08 mg, B7) for (B), and from (67.04 ± 0.05 mg, M9) to (70.13 ± 0.09 mg, M7) for (M). All formulations were within pharmacopeia specification for weight variation none of the tablets deviated from the average weight by more than 10% [26].

The average thickness of ODTs was found to be in the range from (2.92 ± 0.04 mm, B3) to (3.08 ± 0.04 mm, B5) for (B) and from (2.92 ± 0.06 mm, M6) to (3.11 ± 0.09 mm, M7) for (M). It was noticed that all ODTs of both drugs, showed acceptable friability according to the British Pharmacopeia [27], except B1, B2, B3, and B9 for (B), and M2, M6, M8 and M9 for (M) which had friability > 1% **Table 5**, **6**.

TABLE 3: RESULT OF EVALUATION FLOW PROPERTIES OF POWDER FOR SELECTED FORMULAE

	Tapped density (g/cm^3)	Bulk density (g/cm^3)	H Ratio (HR)	Carr's (CI)
Baclofen	0.364 ± 0.030	0.200 ± 0.027	1.818 ± 0.019	45 ± 0.04
(B) With Pro HD 90	0.658 ± 0.021	0.480 ± 0.021	1.370 ± 0.020	27 ± 0.015
(B) With F-melt	0.675 ± 0.042	0.560 ± 0.043	1.205 ± 0.032	17 ± 0.012
(B) With Lactose	0.417 ± 0.020	0.300 ± 0.022	1.389 ± 0.029	28 ± 0.021
(B) With Pro ODT	0.767 ± 0.011	0.637 ± 0.015	1.205 ± 0.021	17 ± 0.023
(B) With Ph. Brust	0.569 ± 0.031	0.495 ± 0.029	1.149 ± 0.034	13 ± 0.021
(B) With Pro SMCC 50	0.466 ± 0.028	0.340 ± 0.025	1.370 ± 0.029	27 ± 0.023
(B) With Pro Easy SP	0.506 ± 0.023	0.420 ± 0.019	1.205 ± 0.021	17 ± 0.012
(B) With Pro Nutra	0.593 ± 0.031	0.433 ± 0.035	1.370 ± 0.017	27 ± 0.026
(B) With Ludiflash	0.592 ± 0.034	0.450 ± 0.030	1.316 ± 0.019	24 ± 0.014

TABLE 4: RESULT OF EVALUATION FLOW PROPERTIES OF POWDER FOR SELECTED FORMULAE

	Tapped density (g/cm^3)	Bulk density (g/cm^3)	H Ratio (HR)	Carr's (CI)
Meloxicam	0.500 ± 0.021	0.300 ± 0.019	1.667 ± 0.023	40 ± 0.019
(M) With Pro HD 90	0.623 ± 0.018	0.480 ± 0.015	1.299 ± 0.017	23 ± 0.014
(M) With F-Melt	0.644 ± 0.013	0.560 ± 0.011	1.149 ± 0.015	13 ± 0.021
(M) With Lactose	0.395 ± 0.027	0.300 ± 0.023	1.316 ± 0.018	24 ± 0.027
(M) With Pro ODT	0.749 ± 0.029	0.637 ± 0.025	1.176 ± 0.024	15 ± 0.015
(M) With Ph. Brust	0.596 ± 0.015	0.495 ± 0.013	1.205 ± 0.011	17 ± 0.023
(M) With Pro SMCC 50	0.453 ± 0.029	0.340 ± 0.023	1.333 ± 0.029	25 ± 0.017
(M) With Pro Easy SP	0.525 ± 0.022	0.420 ± 0.019	1.250 ± 0.031	20 ± 0.026
(M) With Pro Nutra	0.555 ± 0.025	0.433 ± 0.020	1.282 ± 0.024	22 ± 0.028
(M) With Ludiflash	0.616 ± 0.019	0.450 ± 0.014	1.370 ± 0.021	27 ± 0.018

The hardness values for all tested tablets were within (4.07 ± 1.01 kg, B4) to (5.37 ± 0.74 mm, B7) for (B) water-soluble drug and from (4.0 ± 0.1 kg, M6) to (6.23 ± 0.21 kg, M5) for poor water soluble drug (M). This hardness comparatively considered low hardness but provided adequate strength and porosity to ensure short wetting and disintegration time of the tablets. The average drug content of each formula ranged from (87.04 ± 0.01 %, B4) to (114.0 ± 0.02%, B2) for (B) water-soluble drug, and from (90.31 ± 0.03 mg, M5) to (99.21 ± 0.007 mg, M8) for poor water soluble drug (M). Thus, all formulations complied with the Pharmacopeial limits [26].

It was observed that the WT of ODTs ranged from (7.90 ± 0.10 sec, B5) up to (70.03 ± 0.06 sec, B5) for (B) and from (5,57 ± 0.51 sec, B7) up to (35.53 ± 0.5 sec, B3). *In-vitro* disintegration of M3, B3 (F-melt) showed melting from the edge of ODTs, M5 showed ODTs capping, while M6, B6 (Prosolv ODT) showed relatively long disintegration time (120 ± 0.36, 180.10 ± 0.10 sec) correspondingly. The disintegration time varies from (8 ± 0.06 sec, M7) up to (180 sec, M2) for (M) formulae and from (9.10 ± 0.17 sec, B8) up to (180.10 ± 0.10 sec, B6) for (B) formulae with a good correlation with wetting time. All B-ODTs showed dissolution profile 100% within (2-5 min) except B2 showed floating of ODTs and no dissolution.

Dissolution data for M-ODTs illustrated in **Fig. 1** and **Fig. 2**. In SSF, M1 ODT gave higher initial dissolution; 1min (37.129 ± 0.00579%) and at 30 min M4 (97.916 ± 0.00511%), while the amount of Meloxicam dissolved after 10 min (Q10) was used as a parameter to compare different ODT formulations. The figures showed that M9 attained the highest (Q10) value (100.45 ± 0.004%), whereas M5 showed the lowest (Q10) value (45.19 ± 0.008%) and M2 showed no dissolution and floating on the surface of media. F-melt® Grade C used in this study was a spray- dried product composed of xylitol (40-90%), crospovidone (5-40%) and calcium hydrogen phosphate (1-30%) with a mean particle size between 100-130 μm.

It provides a good mouthfeel, stability, flow, tablet hardness, low friability, and high drug loading. It does not cause sticking or capping problems. It was designed for manufacturing orally disintegrating tablets [28] formulae B3, M3 (F-melt®) gave very close and acceptable result of evaluation tests of ODTs, except the friability >1% for B3 (water soluble) while zero% for M3, in addition to the value of Q10, were (70% for M3) while (100% for B3). It might be resulting from the difference in the nature of both drugs. The obtained results are in harmony with that detected by Kumar *et al*., who demonstrated that ODTs batch prepared with F-melt® gave the fastest disintegration and wetting time but friability was greater than 1% [29] **Table 5**, **6** and **Fig. 1**, **2**.

TABLE 5: PHYSICAL EVALUATION OF THE ODT FORMULATIONS USING DIFFERENT CO-PROCESSED EXCIPIENTS WITH WATER-SOLUBLE DRUG (B)

Formula	Weight (mg) ± (SD)	Thickness (mm) ± (SD)	Friability (%)	Hardness (kg) ± (SD)	Drug content (%) ± (SD)	Wetting time (s) ± (SD)	Disintegration time (s) ± (SD)
B1	67.03 ± 0.05	3.04 ± 0.05	0.0	4.12 ± 0.11	89.76 ± 0.02	41.07 ± 0.06	54.90 ± 0.10
B2	68.88 ± 0.04	3.02 ± 0.06	1.471	4.10 ± 0.30	114.55 ± 0.02	29.93 ± 0.12	44.07 ± 0.12
B3	68.07 ± 0.05	2.92 ± 0.04	0.0	5.10 ± 0.56	89.0 ± 0.05	39.90 ± 0.10	80.07 ± 0.12
B4	68.06 ± 0.08	2.97 ± 0.05	0.493	4.07 ± 1.01	87.04 ± 0.01	35.07 ± 0.12	19.90 ± 0.17
B5	68.82 ± 0.04	3.08 ± 0.04	0.971	4.97 ± 0.31	95.65 ± 0.08	7.90 ± 0.10	18.63 ± 0.12
B6	68.10 ± 0.08	2.98 ± 0.09	0.493	5.0 ± 0.40	90.47 ± 0.05	70.03 ± 0.06	180.10 ± 0.10
B7	70.26 ± 0.08	3.05 ± 0.05	0.717	5.37 ± 0.74	98.19 ± 0.008	14.90 ± 0.10	18.83 ± 0.15
B8	69.99 ± 0.07	3.04 ± 0.05	0.576	4.7 ± 0.36	110.5 ± 0.08	16.87 ± 0.15	9.10 ± 0.17
B9	67.02 ± 0.04	3.05 ± 0.05	2.956	4.63 ± 0.25	111.6 ± 0.01	60.07 ± 0.12	80.10 ± 0.10

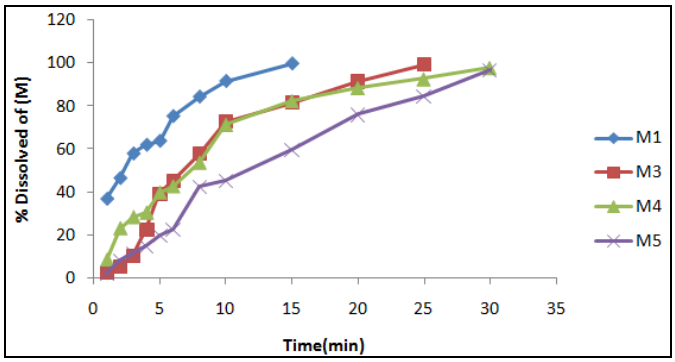

FIG. 1: *IN-VITRO* DISSOLUTION PROFILES OF PREPARED ODTS (M1, M3, M4, M5) USING DIFFERENT CO-PROCESSED EXCIPIENTS WITH POOR WATER SOLUBLE DRUG (M)

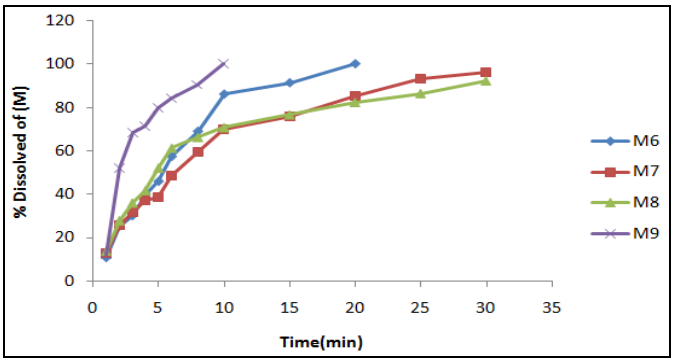

FIG. 2: *IN-VITRO* DISSOLUTION PROFILES OF PREPARED ODTS (M6, M7, M8, M9) USING DIFFERENT CO-PROCESSED EXCIPIENTS WITH POOR WATER SOLUBLE DRUG (M)

TABLE 6: PHYSICAL EVALUATION OF THE ODT FORMULATIONS USING DIFFERENT CO-PROCESSED EXCIPIENTS WITH WATER-SOLUBLE DRUG (M)

Formula	Weight (mg) ± (SD)	Thickness (mm) ± (SD)	Friability (%)	Hardness (kg) ± (SD)	Drug content (%) ± (SD)	Wetting time (s) ± (SD)	Disintegration time (s) ± (SD)
M1	67.06 ± 0.08	3.09 ± 0.06	0.0	4.70 ± 0.26	96.74 ± 0.037	3.5 ± 0.50	13.50 ± 0.68
M2	68.07 ± 0.08	3.02 ± 0.04	1.471	4.87 ± 0.15	94.51 ± 0.049	24.50 ± 0.50	>180
M3	68.04 ± 0.07	3.01 ± 0.03	0.0	4.27 ± 0.25	95.01 ± 0.074	35.53 ± 0.50	80.00 ± 0.35
M4	68.07 ± 0.09	3.01 ± 0.03	0.667	4.33 ± 0.15	95.75 ± 0.032	8.57 ± 0.51	13.85 ± 0.95
M5	68.02 ± 0.09	3.05 ± 0.05	0.714	6.23 ± 0.21	90.31 ± 0.037	10.60 ± 0.53	15.50 ± 0.50
M6	68.95 ± 0.05	2.92 ± 0.06	1.460	4.00 ± 0.10	95.01 ± 0.044	21.53 ± 0.51	120 ± 0.36
M7	70.13 ± 0.09	3.11 ± 0.09	0.730	5.07 ± 0.21	98.22 ± 0.012	5.57 ± 0.51	8.0 ± 0.06
M8	69.90 ± 0.08	3.08 ± 0.06	1.379	5.13 ± 0.15	99.21 ± 0.007	12.60 ± 0.53	10.50 ± 0.58
M9	67.04 ± 0.05	2.97 ± 0.07	2.837	4.2 ± 0.20	93.77 ± 0.06	15.90 ± 1.01	80.0 ± 0.06

Pharmaburst® 500 contains (mannitol, sorbitol, crospovidone, precipitated silicone dioxide) [30]. No significant difference between Pharmabrust®-ODTs Baclofen and Meloxicam through all their evaluation test result, all test of ODTs within acceptable range except the friability >1% for B (water soluble) while zero% for M, Q10 value were up to 90% and 100% release at first 10 mint for M1 and B1 respectively. Although WT and DT data of both drug within acceptable range but the time required for wetting, and disintegration of B1-ODTs (water soluble) is higher than the M1-ODTs (poor water soluble), this result complies with Moqbel *et al*., [31] whereas the WT, DT became

inversely proportion with increasing of Pharma-burst® 500 ratios added to poor water-soluble drug, in another side the long WT and DT for B1-ODTs may be caused by reaching out saturated solubility of a small volume of SSF in both WT and DT test, the solution contained a much solute possible of (B-water soluble), accompanied by the presence of water-soluble co-processed excipient (Pharma-brust® 500) **Table 5**, **6** and **Fig. 1**, **2**.

Ludiflash® composed of mannitol (90%), Kollidon® CL-SF (crospovidone) (5%), and Kollicoat® SR 30D (polyvinyl acetate dispersion) (5%) [32]. B2 and M2-ODTs (Ludiflash®) showed highly friability 1.471%>1% for both drug and long DT (44.07 ± 0.12 sec, B2), (>180 sec, M2), it was noticed that no dissolution was achieved after 30 min, under the specified dissolution conditions. Even though using two different drug's properties This could be referred to Ludiflash® prevent contact of ODTs with the dissolution medium caused floating on the surface it might be because the Ludiflash® content (crospovidone and polyvinyl acetate) do not dissolve completely in water, nor is it entirely soluble in organic solvents (Data from manufacturer). The long disintegration time of Ludiflash- ODTs were exhibited relatively comparing to other formulae, although it possesses the same composition as Pharmaburst. Similar outcomes were observed by Shamma & Basha [33].

The failed in dissolution up to 30 min of Ludiflash formulae compared with other formulae could be attributed to the presence of the extended release excipient Kollicoat SR 30D in its composition. Kollicoat is a commonly used material for the coating and preparation of sustained release dosage forms [34] **Table 5**, **6** and **Fig. 1**, **2**.

For high functionality excipients (Prosolv HD 90®, Prosolv SMCC 5O®, Prosolv ODT G2®, Prosolv EASYtab SP®, and ProsolvEASYtabNutra®) the results showed B4, M4- ODTs (Prosolv HD 90®), B5, M5-ODTs (Prosolv SMCC 50®), B7, M7-ODTs (Prosolv EASYtab SP®) and B8, M8-ODTs (ProsolvEASYtabNutra®) gave acceptable result in all ODTs evaluation test and with short WT and DT except the friability of M8-ODTs were higher than 1% , and the drug concentration was less than 70% at 10 min. The results emphasized that Prosolv SMCC 5O® co-processed consists of cellulose excipients which is microcrystalline cellulose (binder) in addition to colloidal silicon dioxide (a glidant) with improved flow and compaction features [35] with average particle size 65 (µm), whereas Prosolv HD® 90 is a new grade of silicified microcrystalline cellulose of high density develops by silicification of Avicel® PH-302. [36] The manufacturer declares the following characteristics bulk density 0.35-0.50 g/mL; tapped density-0.45-0.68 g/mL; and particle size 125 (µm). The results noticed that each excipient mentioned before gave the short WT and DT with both B, and M accompanied with 100% release of drug with B4, B5 (water soluble) within 2-5 min while the results for M representing poor water soluble drug were (71.51 ± 0.00445, M4) and (19 ± 0.008, M5) at 10 min. These results may be due to the effect of silicification of microcrystalline cellulose forming the strong compact with highly binding materials with low water affinity which is not suitable with poorly water-soluble drugs because water accessibility to the compact are prohibited and thus, drug dissolution is delayed, this result complies with Rojas & Kumar 2012 [37]. The effect of silicification on the tableting performance of microcrystalline cellulose prove the decrease of percent of drug release with silicified microcrystalline cellulose compared with non-silicified one using griseofulvin (poorly water soluble) as drug model **Table 5**, **6** and **Fig. 1, 2**.

ProsolvEASYtab SP® made by co-processing microcrystalline cellulose (a dry binder), colloidal silicon dioxide (a glidant), sodium starch glycolate (a disintegrant), and sodium stearyl fumarate (a lubricant) at 96.5:2:1:0.5 ratios, with average particle size 140 (µm) [38]. Although Prosolv EASY tab SP® gave short DT, and WT which may be related to the presence of a disintegrant in its components, but it was observed delaying of drug release (96.26 ± 0.0078%) at 30 mint. This due to sodium stearyl fumarate (SSF) is Fatty acid esters lubricant [39] had some negative effects on the in vitro dissolution of immediate-release tablets, effect of lubricants on dissolution is due to their large surface area which, in combination with their hydrophobicity, hinder water penetration from affecting dissolution. This result was remarkable with M(poor water soluble) comparing with B (water soluble) **Table 5**, **6** and **Fig. 1**, **2**.

ProsolvEASYtabNutra® obtained SPI pharma (Wilmington, DE, USA) the data supplied from manufacturer declared that ProsolvEASYtab Nutra® is All-in-One, Ready-to-Use Excipient Composite: binder, glidant, super disintegrant, and lubricant. Microcrystalline cellulose, colloidal silicon dioxide, croscarmellose, palm kernel oil saturated, DATEM, with Average particle size 130 (µm) Prosolv® EASY- tab- Nutra is a high functionality pre-lubricated excipient (inactive ingredient) composite made specifically for direct compression nutraceutical applications. It was found that ProsolvEASYtabNutra® had short DT and WT which is resulting from croscarmellose sodium that characterized as superdisintigratnt composed of a cross-linked polymer of carboxymethylcellulose had the high swelling capacity, effective at low concentration (0.5-2.0 can be used up to 5.0%) [40]. DATEM (di-acetyl tartaric ester of monoglycerides) is anionic emulsifiers amphiphilic nature and generally used in bakery products [41]. EASYtab Nutra exhibits the same advantages as EASYtab SP and is suitable for nutraceutical applications. Active ingredients simply need to be added to EASYtab Nutra and can be added directly on the tablet press. Simplifies tableting, no need for further excipients. In ProsolvEASYtab Nutra® -ODTs it was noticed delaying in % of drug release (92.407 ± 0.0063%) after 30 min **Table 5**, **6** and **Fig. 1**, **2**.

In Contrast, the results of Prosolv ODT G2® -ODT evaluation test gave long DT (180s,120s) for B6 (water soluble) and M6 (poor water soluble) respectively with the highest drug percent release approximately (86.12 ± 0.008%) at first 10 mints. Prosolv ODT G2® is consisting of complex of soluble and insoluble ingredients (MCC, colloidal silicon dioxide, mannitol, fructose, crospovidone) [42]. Long WT might be resulting from the presence of a complex composition containing additional microcrystalline cellulose (MCC), and fructose affects the SWT time. The presence of MCC led to a decrease in the wetting of the low-substituted hydroxy-propyl-cellulose tablets and the increase in MCC content led to an increase in the wetting time of the prepared tablet. Prosolv ODT G2® complex probably the reason for its disintegration delay (>180 s) especially MCC which lowers the water uptake into the tablet [43]. The highest percent of drug release whether for B and M, might be due to the average particle size measuring by laser diffraction (52 µm) which in order increase total surface area of solid interact with surrounded dissolution media and hence, increase the percent of drug release compared with other For high functionality excipients **Table 5**, **6** and **Fig. 1**, **2**.

Prosolv ODT, Ludiflash, and Pharmaburst are mannitol-based excipients together with crospovidone as a super disintegrant, obtained results regarding SWT were quite different. All formulae prepared using Prosolv ODT and Ludiflash had relatively long disintegration time for both different drug properties B, and M. this result could be attributed to the presence of a mixture of sorbitol and mannitol in Pharmaburst compared to mannitol alone in Prosolv ODT and Ludiflash confirming the favorable hydration capacity of sorbitol due to the presence of equatorial OH on the C-2 atom resulting in more hydration and high wetting capacity in contrary to mannitol having an axial OH on C-2 atom. A possible rationalization of the axial/equatorial effect could be in consideration of the crystal packing of the molecules. There is a preference for equatorial OH groups to have two hydrogen bonded contacts, compared to axial OH which tends to have only one hydrogen bond. This result complies with Tayel *et al*., 2016 [44] **Table 5**, **6** and **Fig. 1**, **2**.

The result of B9, M9- ODTs (Lactochem® Microfine) is nearly identical; all quality control test for ODTs gave the acceptable result except the friability which is >1% despite the drug nature. With 100% drug release for within 2-5 min for B (water soluble) and within 10 mint for M (poor water soluble) this result could be referred to the size of Lactochem® microfine which is average (5-10 µm) [45]. By using design expert 10 to select the best formulae of both drugs (water sol and poor water sol) the best formulae were for poor water soluble (M) : M9 (Lactochem ® microfine) > M3 (F-melt®) > M6 (prosolv® ODT) > M1 (Pharma-burst®) for Water soluble: B4 (prosolv® HD 90) > B3 (F-melt®) > B6 (prosolv® ODT) > B1 (Pharmaburst®).

CONCLUSION: F-melt® was suitable to form fast- disintegrating tablets by direct compression method, Pharmaburst®, and Prosolv ODT® also considered a co-process excipients that showed the

optimum results of ODTs evaluation test comparatively with other excipients whether using water-soluble drug or poor water-soluble drug in equal dose, can provide pharmaceutical producer with multifunctional property with cost-saving in drug technology.

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