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Original article

Design of taste masked enteric orodispersible tablets of diclofenac sodium by applying fluid bed coating technology

Hadyah Faleh Alotaibi [a], Samar Elsamaligy [b], Gamal M. Mahrous [a,*], Mohsen A. Bayomi [a], Hanaa Abdelmonem Mahmoud [c]

[a] Department of Pharmaceutics, College of Pharmacy, King Saud University, Riyadh 11451, Saudi Arabia
[b] Department of Pharmaceutics, College of Pharmacy, Helwan University, Ain Helwan, Cairo, Egypt
[c] Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Cairo University, Cairo, Egypt

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ABSTRACT

Diclofenac sodium (DS) a non-steroidal anti-inflammatory drug has a bitter taste and is a local stomach irritant. The aim of this study was to formulate taste masked DS orally dispersible tablets (ODTs) with targeted drug release in the intestine. Pellets of DS were designed using sugar sphere cores layered with DS followed by an enteric coat of Eudragit L100 and a second coat of Eudragit E100 for taste masking. The produced pellets had a high loading efficiency of 99.52% with diameters ranging from 493.7 to 638.9 μm. The prepared pellets were spherical with smooth surfaces on scanning electron microscopy examination. Pellets with the 12% enteric coat Eudragit L100 followed by 5% Eudragit E 100 resulted in 1.4 ± 0.5% DS release in simulated gastric fluid (SGF) and complete dissolution in simulated intestinal fluid (SIF). The pellets were then used to formulate ODTs. *In vitro* disintegration time of ODTs ranged from 20 ± 0.26 to 46 ± 0.27 s in simulated saliva fluid (SSF). Dissolution was less than 10% in SGF while complete drug release occurred in SIF. The release rate was higher for the optimized formulation (F12) in SIF than for the marketed product Voltaren® 25 mg tablets. The optimized ODTs formulation had a palatable highly acceptable taste.

1. Introduction

In recent decades, although most pharmaceutical research sought to develop new dosage forms with quality of life as the focal point, most efforts have been focused on ease of administration. Among the many dosage forms developed to improve the ease of administration is the orally disintegration tablet (ODT). ODTs, the most widely preferred commercial products (Sastry et al., 2000, Bandari et al., 2008, Pahwa et al., 2010, Bhasin et al., 2011), are solid oral preparations that disintegrate rapidly in the oral cavity the *in vitro* disintegration time of ODT is approximately ≤30 s (FDA, 2008).

ODTs have been associated with high patient compliances especially for psychic, geriatric and pediatric patients with a difficulty in swallowing conventional tablets or have no access to water. (Ciper and Bodmeier, 2005; Pfister and Ghosh, 2005; Suresh et al., 2008; Abdelbary et al., 2009). Masking the unpleasant bitterness of drugs is a major challenge in the development of such ODTs.

Diclofenac sodium (DS) a potent non-steroidal anti-inflammatory drug (NSAID) is widely used clinically owing to its anti-inflammatory, analgesic and anti-pyretic effect (Dastidar et al., 2000). The drug has an intensely bitter and burning taste. Like many NSAIDs, DS may cause local stomach irritation. Enteric coating of microcapsules for improved delivery of DS to intestine with cellulose acetate phthalate and ethylcellulose polymers was reported (Biju et al., 2004). Al-Omran et al. (2002) formulated microcapsules with good palatability and improved taste masking of DS using ethyl cellulose with the aid of Avicel and lactose in a coacervation process into spherical cores. Taste masking for fast disintegrating ODTs was also reported using veegum® clay (Sona and Muthulinga, 2011). Thus, combining of masking taste with enteric coating for intestinal drug delivery are therefore an effective features that required to be achieved.

* Corresponding author at: Department of Pharmaceutics, College of Pharmacy, King Saud University, P.O. Box 2457, Riyadh 11451, Saudi Arabia.
E-mail address: gmmarous@ksu.edu.sa (G.M. Mahrous).

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Eudragit® polymers are copolymers derived from esters of acrylic and methacrylic acid, whose physicochemical properties are determined by functional groups (Chang et al., 2009). These polymers are widely used as film formers in application for functional pharmaceutical coatings for controlling the release of drugs and for protective coating (Chang and Hsiao, 1989; Pearnchob and Bodmeier, 2003). To protect the active ingredient from the gastric fluid and to improve drug effectiveness, Eudragit L and S, anionic polymers dissolve at rising pH values, are the preferred choices (Singh et al., 2015; Senthil Kumar et al., 2010), while cationic Eudragit E polymers help to seal sensitive active ingredients and increase patient compliance by masking taste and odors (Joshi, 2013). Even when thin layers of Eudragit are used, the desired effect is achieved, which makes it an extremely economical application. Applying several coatings of Eudragit on tablets or pellets is focused on either achieving enteric coating or time-dependent drug release in targeted drug delivery (Bott et al., 2004).

Many advanced technologies are used in pellet coating such as extrusion-spheronization (Han et al., 2013; Rahman and Ali, 2008) and fluidized bed coater (Bott et al., 2004). In fluidized bed technology, pellets are fluidized followed by spraying with the coating formulation (which are in permanent movement due to a strong air flow), to ensure efficient drying (Jones, 1994). The rapidly produced coated pellets may have high yields with small loss of materials in addition to good flow properties, low friability and homogeneity in drug distribution (Wong et al., 2013). Thus, this technology is highly advantageous and suitable for large-scale production.

In this study, fast disintegrating tablets comprised of DS with properties such as taste masking and specific drug release in the intestine were designed by applying successive coatings of different methacrylates on to DS pellets, that prepared by layering DS on sugar spheres, using the fluid bed coating technology.

1.1. Materials

DS, Croscarmellose sodium (CCS), Crospovidone (CP), PEG 6000, and microcrystalline cellulose (Avicel PH101) were kindly supplied by Riyadh Pharma CO, (Riyadh, KSA). Hydroxypropyl methylcellulose (HPMC) E3 was obtained from Colorcon (Orpington, UK). Mannitol (Mannogem TM EZ) was supplied by SPI (Grand Haven, USA). Eudragit L100, Eudragit E100 were purchased from Evonik Industries AG Pharma Polymers & Services CO (Darmstadt, Germany). Sodium stearyl fumarate (NSF) was purchased from Riedel-de Haën CO (Seelze, Germany). Basic sodium tri-hydrogen orthophosphate, sodium hydroxide, isopropanol, acetone, methanol, and water-soluble dyes were purchased from Merck CO (Darmstadt, Germany). Non-pareils sugar spheres NF, NP Pharm SA, (250–595 μm) were obtained from (Bazainville, France). All other chemicals were of analytical grade and used without further purification.

2. Methods

2.1. Preparation of DS layered sugar spheres using fluid bed coater

Drug-loaded pellets were prepared in a fluid bed coating processor (Mycrolab fluid bed processor; Oystar Huttlin, Germany) using the suspension layering technique. The drug-binder suspensions were prepared by dispersing 71 g of HPMC E3 (that acts as a binding agent and barrier polymer (Chatlapalli and Rohera, 1998)) in 1000 ml of deionized water with constant stirring to obtain a homogenous dispersion. Twenty-five grams of DS was added to the prepared solution with continued stirring at 2000 rpm. The obtained suspension was sprayed onto drug-free sugar spheres (250 g) in the fluid bed processor. The layering conditions were optimized for a batch size of approximately 450–535 g with inlet temperature, 45–60 °C; product temperature, 35–45 °C; air flow, 20–30 m^3/h; nozzle diameter, 1.2 mm; spray pressure, 1.0 bar; atomizing air pressure, 1–1.5 bar; and spraying rate, 2–5 g/min. Samples of pellets (~0.5 g) were taken each hour during processing for evaluation and optimization. The obtained pellets were then dried in the fluid bed for an estimated 2 h at 50 °C to attain a moisture content <2% w/w as tested by a moisture balance. The dried pellets were then sized on a sifter to remove agglomerates, broken pellets and fine powder. The obtained drug-layered pellets were stored in a desiccator pending further processing.

2.1.1. Assay of DS content of drug-layered sugar spheres

An amount of 100 mg of layered pellets was accurately weighed and grinded in a porcelain mortar to achieve a very fine powder that was dispersed in 100 ml of phosphate buffer (pH 6.8). The dispersion was filtered using a 0.45-μm membrane filter, and 1 ml of the filtrate solution diluted to 25 ml with the same buffer in a volumetric flask. The solution was then assayed spectrophotometrically at λ_{max} = 277 nm to determine the DS content. The test was performed in triplicate and the mean absorbance reported ± SD.

For spectrophotometric assay at 277 nm, a calibration curve was constructed. Linearity of the calibration curve was obtained in a concentration range from 1 to 24 μg/ml. Linear equation for standard calibration curve was

$$Y = 0.0333\,X + 0.0086$$

The determination coefficient (R^2) of the standard curve was found to be 0.9993 which established high linearity.

2.2. Enteric coating of DS-layered pellets with Eudragit L100

Eudragit L 100 suspension (enteric coating suspension) was prepared by dissolving 187 g of polymer in half the amount of a mixture of acetone, isopropanol, and deionized water at weights of 266.7 g, 399.9 g, and 33.36 g, respectively. Talc (as anti-adherent, 94 g) and tri ethyl citrate (as plasticizer, 19 g) were also dispersed in the remaining solvent mixture (Evonik, 2009). The two dispersions were then mixed thoroughly using a high shear mixer (2000 rpm). The prepared final suspension was then passed through a 0.5-mm sieve to remove large or aggregated particles. This suspension was used in the fluidized bed coater to achieve 5, 10, 12, 15, and 20% w/w coating based on the drug-loaded pellets. The layering conditions were developed for a batch size of approximately 300–450 g with inlet temperature, 40–55 °C; product temperature, 30–40 °C; air flow, 25–35 m^3/h; nozzle diameter, 1.2 mm; spray pressure, 1.5 bar; atomizing air pressure, 1–1.5 bar; and spray rate, 2–5 g/min. To avoid excess wetting of the core and hence agglomeration during the process, the spraying rate, drying rate, and rate of fluidization with product and inlet temperature were precisely controlled. The coating process continued until the desired coating % was obtained according to the weight of the sprayed suspension. Samples of pellets (~0.1 g) were taken from each process every 15 min to optimize the process parameters. The obtained pellets were then dried within the fluid bed for approximately 2 h at 50 °C to a moisture content <2% w/w using a moisture balance. To verify the reproducibility of the operative procedure, four batches were prepared for each system. Dry pellets were kept in a desiccator pending further processing.

2.3. Coating the enteric-coated pellets with Eudragit E 100 for taste masking

Eudragit E100, the taste masking coating suspension was prepared by dissolving 31 g of polymer in half the amount of a mixture of acetone and isopropanol, 177 g and 266.2 g, respectively. Talc

was used as an anti-adherent to reduce stickiness and prevent agglomeration during the layering process and PEG 6000 used as a plasticizer in weights of 15 g and 9.5 g, respectively. Both materials were dispersed in the remaining solvent mixture (Evonik, 2009). The two prepared solution and suspension were then mixed thoroughly using a high shear mixer (1500 rpm) for 10 min. The layering conditions were developed for a batch size of approximately 300–400 g with inlet temperature, 40–55 °C, product temperature, 30–40 °C, air flow, 25–30 m^3/h; nozzle diameter, 1.2 mm; spray pressure, 2–2.5 bar; atomizing air pressure, 2.5–3 bar; and spray rate 2–5 g/min. The coating process continued until the required coating percentage was obtained by spraying a preweight suspension of the polymer. The obtained pellets were then dried in the fluid bed for approximately 2 h at 45 °C to a moisture content <2%. The pellets were stored in a desiccator pending further processing and characterization.

2.4. Characterization of the prepared pellets

The resulting pellets were evaluated to obtain the yield, drug content, particle size, particle size distribution, surface morphology and *in vitro* drug release in simulated saliva, simulated gastric fluid (SGF) (pH 1.2) and simulated intestinal fluid (SIF) (pH 6.8).

2.4.1. Percentage yield

The pellet yield was determined by accurately weighing the produced pellets. The percentage process efficiency was calculated using the following formula:

$$\%\ \text{Yield} = \frac{\text{practical weight of pellets produced (g)}}{\text{therotical amount used in production (g)}} * 100 \quad (1)$$

2.4.2. Drug content of pellets

An aliquot of the coated pellets of each batch was pulverized to a fine powder in a porcelain mortar. An accurate amount (100 mg) of the powder was weighed and dispersed in 25 ml of pH 6.8 phosphate buffer and the volume was adjusted to 100 ml in a volumetric flask. The dispersion was filtered using a 0.45-μm membrane filter. A volume of 1 ml of filtrate was diluted to 25 ml with the buffer. Drug concentration was measured spectrophotometrically at 277 nm. All tests were performed in triplicates and mean of drug content ± SD calculated. The percentage drug loading efficacy was calculated using the following formula:

$$\%\ \text{drug loading} = \frac{\text{actual amount of drug present in pellets}}{\text{theoretical amount of drug present in pellets}} * 100 \quad (2)$$

2.4.3. Particle size analysis

The particle size and particle size distribution of the formulated pellets were investigated using laser light diffraction (Mastersizer Scirocco 2000, Malvern Instruments; Grove wood Road, UK). For a typical experiment, approximately 300 mg of the pellets were fed into the sample micro feeder. All samples were analyzed 5 times and an average of the results taken. The pellets in the 10th (d (0.1)), 50th (d (0.5)) and 90th (d (0.9)) percentiles were used to characterize the pellet size distribution. The approximate mean diameter was taken as the average of d (0.1), d (0.5), and d (0.9) values.

The span value was employed to characterize the pellet size distribution, where a small span value indicated a narrow particle size distribution as was calculated by the following formula:

$$\text{span} = \frac{D90 - D10}{D50} \quad (3)$$

2.4.4. Morphology and surface properties of pellets using scanning electron microscopy (SEM)

The morphological characteristics and surface properties of different formulated pellets were observed by SEM. The samples were sputter-coated with a thin gold palladium layer under an argon atmosphere using a gold sputter module in a high-vacuum evaporator. The coated samples were then scanned and photomicrographs taken using the Jeol JSM−1600 (Tokyo, Japan).

2.4.5. Release of DS from pellets in Simulated Salivary Fluid (SSF), SGF, and SIF

SSF was prepared by dissolving 13.87 g of potassium dihydrogen phosphate and 35.08 g of disodium hydrogen phosphate in a sufficient amount of water to produce a final volume of 1000 ml with a final pH of 6.8 to mimic the salivary fluid (Mehta et al., 2009). The equivalent of a 25 mg DS dose of the prepared enteric-coated and taste-masked pellets was subjected to a drug release test at 37 °C in 10 ml of SSF for 3 min, with frequent shaking. The amount of drug released was assayed spectrophotometrically in the SSF samples, with any drug released from pellets considered an indication of a bitter taste (this will also be confirmed in the *in vivo* studies).

The *in vitro* release profile of DS from coated pellets in SGF and SIF was performed according to the USP paddle method, dissolution apparatus II. An amount equivalent to 25 mg DS of the coated pellets was used, with all tests conducted in 750 ml of SGF (pH 1.2) made from 0.1 N HCL, for 2 h. The dissolution medium was maintained at 37 ± 0.1 °C with a stirring speed of 50 rpm. Samples of 5 ml were withdrawn at predetermined time intervals, and the same volume of fresh buffer compensated. After 2 h, the medium was changed to SIF (pH 6.8) and was achieved by adding 250 ml of 0.2 M tribasic sodium phosphate and the test continued for additional 2 h. The samples were filtered using a 0.45-μm filter membrane and analyzed spectrophotometrically at 277 nm. Dissolution tests were performed in triplicates for each coated pellet formulation and the % drug release was calculated and reported as mean % ± SD. According to the United States Pharmacopeia and National Formulary USP 32, enteric-coated pellets should not release more than 10% of DS within 2 h in SGF.

2.5. Formulation of DS pellets into ODTs

Various formulations of DS pellets were designed for the preparations of ODTs with the characteristics of taste masking and the enteric effect. The prepared pellets mixed with suitable excipients were compressed into ODTs with the required properties. Pellets were mixed with either CP or CCS as superdisintegrants at three different levels: 2.5, 5, and 10% w/w. The composition of the different pellet-excipient blends for compression into 200 mg tablets is shown in Table 1.

The amount of pellets equivalent to 25 mg of DS, MCC, colloidal silicone dioxide (CSD), mannitol as well as one of the superdisintegrants was accurately weighed and transferred into a cube mixer and mixed for 5 min. The weighed amount of NSF was then mixed with the powder blend in the mixer for a further 5 min. Prior compression, followability and compressibility Index for the powder blends were evaluated. Angle of repose was determined by the funnel method (Ma and Hadzija, 2013). The Carr's compressibility index was calculated based on the bulk and tapped volumes (Aguilar-de-Leyva et al., 2011). The pellet-excipient blends were directly compressed into 200 mg tablets using a flat 9 mm single punch (Tablet press, Erweka, Germany). The compression force of the tablet machine was adjusted to yield tablets of hardness ranging between 3 and 3.75 kg. The formulated ODTs were subjected to evaluation tests and then stored in an air-tight high-density polyethylene container for further characterization.

Table 1
Composition of Pellets and excipients (mg) compressed into 200 mg DS ODT Formulations.

Formula code	DS in pellets	MCC	NSF	CSD	CCS	CP	Mannitol
F1	25	20	4	1	5		98
F2	25	20	4	1	10		93
F3	25	20	4	1	20		83
F4	25	20	4	1		5	98
F5	25	20	4	1		10	93
F6	25	20	4	1		20	83
F7	25	20	4	1	5		90
F8	25	20	4	1	10		85
F9	25	20	4	1	20		75
F10	25	20	4	1		5	90
F11	25	20	4	1		10	85
F12	25	20	4	1		20	75

DS: diclofenac sodium, MCC: microcrystalline cellulose, NSF: sodium steryl fumarate, CSD: colloidal silicon dioxide, CCS: croscarmellose sodium, CP: crospovidone. F1–F6 used 12% Eudragit L100 coated pellets, F7–F12 used double coated pellets, double coat was 12% Eudragit L100 and 5% Eudragit E100. Final weight of each tablet equal 200 mg

2.6. Evaluation of DS ODTs

2.6.1. Weight variation

The weight variation test was carried out according to BP to ensure uniformity in the weight of the prepared tablets. Twenty tablets from each batch formulation were randomly selected and accurately weighed, individually, using a digital balance; their average weight was calculated and reported as mean ± SD.

2.6.2. Friability test

The tablet friability test was conducted according to the United States Pharmacopeia and National Formulary USP 32 using an Erweka Friability tester.

2.6.3. Tablet hardness and thickness

Ten tablets were randomly selected and individually measured for their thickness using a micrometer, and then tested for hardness using a Hardness Tester (Hardness tester, Erweka). The average thickness and average hardness values ± SD were reported.

2.6.4. Drug content

Ten randomly selected tablets from each formula were individually assayed for drug content uniformity as described under the drug content of pellets.

2.6.5. In vitro disintegration time in SSF

The disintegration time of tablets was measured using the following modified procedure described by Gohel et al. (2004). Ten milliliters of SSF prepared at 25 ± 0.1 °C was placed in a 10 cm petri dish. One tablet was carefully positioned in the center of the petri dish and the time required for the tablet to completely disintegrate into fine particles was recorded using a digital stop watch to the nearest second. Only one ODT was tested each time. All results are presented as mean ± SD (n = 6).

2.6.6. In vitro dissolution study

The *in vitro* dissolution tests for DS ODTs were performed according to USP32 using a dissolution tester (DH 2000 ERWEKA, Heusenstamm, Germany). Dissolution was performed in 750 ml pH 1.2 (0.1 N HCl) for 2 h followed by changing of the dissolution media to pH 6.8 phosphate buffer for an additional 2 h. The change in pH was achieved by adding 250 ml of 0.2 M tribasic sodium phosphate. The paddle speed was adjusted to 50 rpm. The temperature of the dissolution medium was maintained at 37 ± 0.5 °C throughout the experiment. Samples of 5 ml were withdrawn and filtered through a 0.45-μm filter at suitable time intervals. Each withdrawn sample was replaced with 5 ml of dissolution media. The DS content of each collected samples was analyzed at 277 nm using pH 6.8 phosphate buffer as blank. The cumulative percentage of dissolute drug was plotted against time. The *in vitro* dissolution profiles of DS from selected formulations of ODTs were compared to that of the commercial Voltaren® 25 mg tablet.

2.7. In vivo disintegration time and taste evaluation

This study was performed for two selected formulations denoted code A (double polymer-coated pellets of 12% Eudragit L100 followed by 5% Eudragit E100) and code B (single polymer-coated pellets of 12% Eudragit L100 pellets). The protocol for this work was accepted by the Institutional Human Ethics Committee of Pharmacy College, King Saud University, Riyadh, Saudi Arabia. The study was performed using 10 female healthy volunteers between ages 20–40 and each volunteer received a code representing their initials. Volunteers allergic to NSAID or having any acute or chronic gastrointestinal diseases were excluded from the test. All volunteers were informed of the objective of the study and provided with a copy of the instructions before the start of the study. Each subject read, understood and gave written informed consent. Each volunteer was allowed to take one tablet via mouth (after mouth rinsing) without swallowing the tablet. Volunteers were instructed to move the tablet against the upper palate of the mouth with their tongue and to trigger a gentle tumbling action on the tablet, without biting on it. A time between 30 and 60 s was allowed for the tablets to completely disintegrate. The volunteer had to then remove the tablet via spitting (without washing the mouth). The time required for complete disintegration was recorded. After spitting, the volunteers had 5 min to record their feedback. The selected formulas were subjected to evaluations for bitterness, grittiness, *in vivo* disintegration time, after taste and overall acceptability. Bitterness was recorded according to the bitterness intensity scale from 1 to 4 where 1, 2, 3, and 4 indicated "not at all bitter", "slightly bitter", "highly bitter", and "extremely bitter", respectively. Only scores of 1 or 2 for the taste were considered acceptable. After 15 min, the volunteer was allowed to wash the mouth cavity with a glass of water. One tablet was taken each time with a 30-min time interval between two evaluations for the same volunteer.

All results are expressed as mean ± (SD). Statistical analysis was performed using the student *t*-test or one-way analysis of the variance with $p \leq 0.05$ as the significant level; Instate software was used for the statistical analysis.

3. Results and discussion

3.1. Preparation of pellets:

Owing to its high drying capacity when coating inert cores and particles that tend to agglomerate in wet conditions, fluidized bed technology was selected for use in this study. Many parameters

affect film formation and are highly dependent on the characteristics of a given polymer (Srivastava and Mishra, 2010). Therefore, optimizing the processing conditions for pellet development had to be performed for the selected polymers. Initially, sugar spheres were successfully layered into pellets with DS using a fluid bed coater. HPMC, a commonly used binder for pellet preparation, was selected as the binder for drug layering to ensure the drug particles could attach to the surface of the sugar spheres to ultimately result in uniform drug layers (Kumari et al., 2013). After drug layering, our aim was to achieve 40% w/w drug loading. The pellets were therefore polymer-coated and designed to accommodate different percentages of the enteric coat, Eudragit L100; at percentages of 5, 10, and 12% w/w. When the 15 and 20% coatings were tested, uniform pellets with acceptable reproducibility were not achieved. However, the fluid bed coater using the Eudragit L100 coating of DS-layered sugar spheres was successful using the following optimized parameters: inlet temperature, 40–55 °C; product temperature, 30–40 °C; air flow, 25–35 m^3/h; nozzle diameter, 1.2 mm; spray pressure, 1.5 bar; atomizing air pressure, 1–1.5 bar; and spray rate, 2–5 g/min. Similar conditions were used for the Eudragit E100 coating with two exceptions: spray pressure, 2–2.5 bar; and atomizing air pressure, 2.5–3 bar. Successful coating was considered when each 15-min sample did not exhibit agglomeration and displayed freely flowing properties. A coat of Eudragit E100 (taste mask) was applied using the least possible coating percentage of 5%, as this was sufficient to ensure a uniform homogenous polymer coat on the surface of the Eudragit L100-coated drug-layered sugar spheres of the selected particle sizes.

3.2. Evaluation of pellets

3.2.1. Measurement of drug content, EE% and % yield of the DS-layered sugar spheres

Drug content (%), also denoted as drug loading %, was determined by a drug assay using phosphate buffer (pH 6.8). When the fluid bet coater was used, 39.7 ± 0.41% was achieved for the drug content after layering the sugar sphere with DS and using HPMC as a binder in the suspension. The calculated EE% was 99.25%. This high value indicated that the percentage of drug loss during the layering process was very low (0.75%); thus, demonstrating the great advantage of applying the fluidized bed coating technology. The % yield was as high as 86% based on the theoretical amount used, a value beneficial when considering large-scale production.

3.2.2. Measurement of DS content in Eudragit-coated pellets

DS content values for 5, 10, and 12% Eudragit L100 coated and double-coated (12% Eudragit L100 and 5% Eudragit E100) pellets were 37.7 ± 0.33, 35.8 ± 0.32, 35.0 ± 0.29 and 31.1 ± 0.33%, respectively. Drug content was highest at 5% coating and lowest at double coating due to the increase in added coating polymer levels as shown in Table 2.

3.2.3. Determination of pellet particle size

The particle size of pellets after each coating process was determined to derive the pellet properties and the results are presented in Table 2. Generally, the mean diameter of the pellets ranged from 493.74 to 638.90 μm. Evidently, the drug-layered sugar spheres had diameters significantly larger than the initial sugar spheres. Increasing % of polymer coating or adding a double coat is therefore associated with an increase in particle diameter.

The span values were employed to characterize the particle size distribution of the pellets. The calculated span values were small and between 0.62 and 1.0, indicating a narrow particle size distribution (Ibrahim, 2013; Dyankova et al., 2016). The polymer-coated pellets, even at high coating %, displayed a narrow particle size distribution. This might be indicative of the achievement of an efficient and uniform coating process using the fluidized bed coater method at proper conditions, and in the presence of the used plasticizer.

Table 2
Volume weight mean diameters, span values of different DS pellets formulae and their drug contents.

Pellets formulae	Volume mean weighted (μm)	Span values	Drug content % (n = 6)
Sugar sphere	431.19	0.771	
Layered DS pellets	493.74	0.62	39.7 ± 0.40
5% coated pellets	547.87	0.838	37.7 ± 0.33
10% coated pellets	562.04	1.0	35.8 ± 0.32
12% coated pellets	619.63	1.0	35.0 ± 0.29
Double coated*	638.89	0.931	31.1 ± 0.33

* Double coat were 12 %Eudrgit L100 and 5%Eudragit E100.

3.2.4. Examination of morphology and surface properties of prepared pellets using SEM

The morphology and surface properties of the sugar sphere, drug-layered pellets and polymer-coated pellets were examined using SEM.

Fig. 1 shows that sugar spheres possess nearly spherical shape with rough surface, while the layered and coated pellets were more spherical with smoother surfaces. The pellets were also discrete and generally, devoid from cracks. Possessing a smooth surface is a great advantage when using the fluid bed coater as it produces pellets of good followability and suitability for compression into tablets, especially for use in large-scale manufacturing processes.

3.3. In vitro release of DS from coated pellets

The pellets were coated using the enteric coating polymer, Eudragit L100, that should not dissolve in SGF (pH 1.2) as this will retard DS release in the acidic medium. Coating at varying % of Eudragit L 100 was imperative to ensure the effectiveness of the pellets' coating in delaying drug release in the acidic medium before the application of the second coat (Eudragit E 100 polymer; taste masking). The percentage of DS release from 5, 10, and 12% enteric coating and double-coated pellets in SGF for 2 h were only 8.2 ± 0.9, 5.3 ± 1.1, 2.5 ± 0.8 and 1.4 ± 0.5%, respectively (Fig. 2). This indicated the efficiency of enteric coating where less than 10% drug release was observed. Furthermore, as the coating level increased, drug release in the acidic medium became even smaller resulting in only 2.5 ± 0.8% drug release obtained at 12% Eudragit L l00 for enteric coating. Apparently, a second coat with the 5% taste masking Eudragit E100 showed non-significant change in drug release, a value of 1.4 ± 0.5%.

Evidently, from Fig. 2, efficient drug release was obtained in SIF (phosphate buffer, pH 6.8). The drug release from pellets at this pH is due to swelling; thus, dissolving Eudragit L100 film results in water penetration into pellets and drug dissolution. In addition, we observed that DS release from pellets with the 5% enteric coating polymer was faster than that of 10 and 12%. However, the release from doubled coated pellets with Eudragit E100 as the second coat on the pellet's surface is expected to dissolve in SGF as an acid soluble polymer (Leopold and Eikeler, 1998). Accordingly, a second coat was demonstrated to have no influence on drug release in SIF.

3.4. In vitro release of DS from coated pellets in SSF

To ensure the effectiveness of polymer coating with Eudragit L100 (5, 10, and 12%) and Eudragit E100 in controlling the release

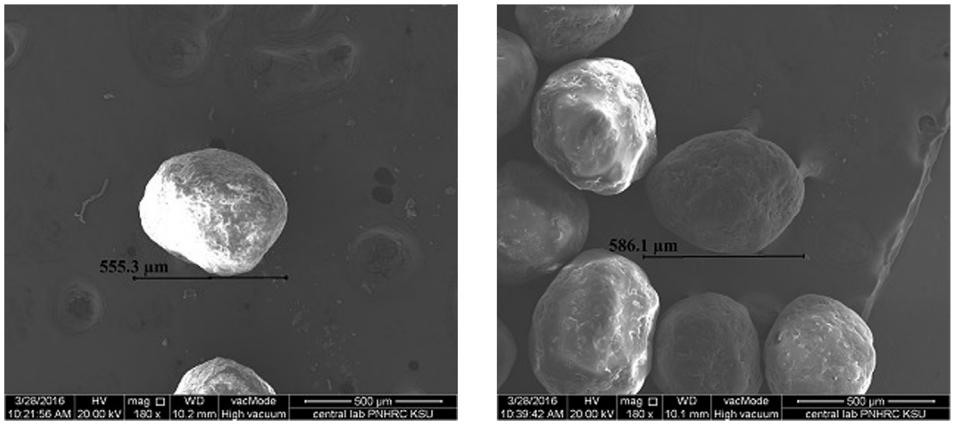

Fig. 1. Scanning electron microscope photos at X300 magnification for pellets of (A) 12% Eudragit L100 coated pellets; (B) double coated pellets.

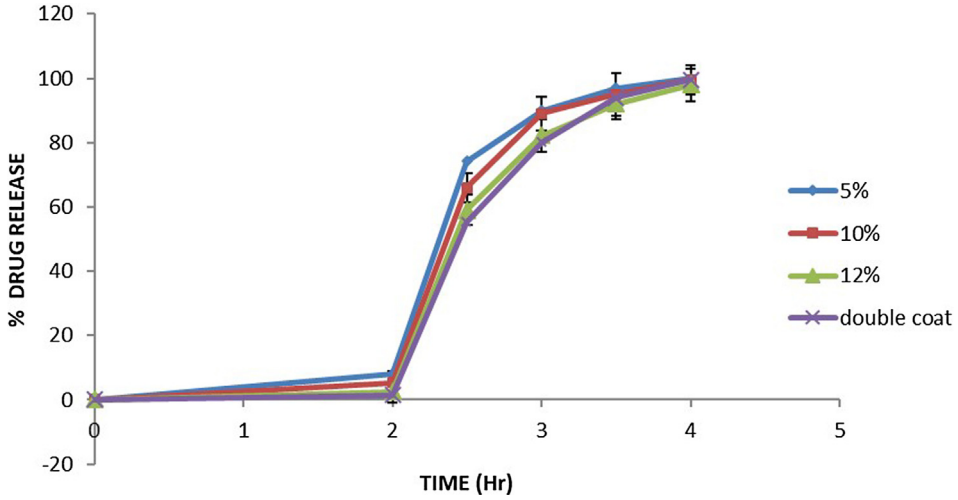

Fig. 2. *In vitro* release of diclofenac sodium (DS) from enteric coated pellets using Eudragit L 100 for 2 hrs in 0.1 N HCL (pH1.2) and for 2 more hrs. in phosphate buffer (pH 6.8) at 37 ± 0.5 °C.

of DS from pellets placed in the mouth, DS release in simulating saliva was tested using all formulated pellets; the final coat of Eudragit E 100 in the double-coated pellets was expected to retard the DS release in SSF (pH 6.8). The Eudragit L100-coated pellets were also tested as it is possible to mask the taste, to some extent, especially at high coating levels. All coated pellets were therefore tested in SSF to detect any possible release of the bitter-tasting DS.

Based on the dissolution in SSF, enteric coating of pellets up to 12% was insufficient to highly retard DS release. The release of DS from coated pellets was 49.8 ± 6.12, 44.06 ± 2.85 and 31.75 ± 1.20% at 5%, 10% and 12% Eudragit L100 coating, respectively. This high % of DS in SSF indicates an unpleasant taste of the pellets if present in mouth when in contact with saliva. This made it necessary to add a second coat of Eudragit E100 at 5%, the least possible percentage, to retard the release of DS in SSF, accordingly masking the bitter taste of the drug. The release of DS from double-coated pellets of 12% Eudragit L100 and Eudragit E100 as taste masking polymers, was as small as 3.0 ± 0.11% compared to 31.75% for a single coat of 12% Eudragit L100.

3.5. Formulation and physical evaluation of DS ODTs

To prepare ODT tablets, we selected the most promising coated pellets that showed minimum DS release within 3 min in SSF and fast dissolution in SIF. The selected pellets were the DS-layered sugar spheres coated with 12% Eudragit L100 (enteric-coated) and pellets double-coated with 12% Eudragit L 100 and 5% Eudragit E (enteric-coated and taste-masked). These pellets were mixed with excipients to prepare the ODT. Some pharmaceutical scientists depend on ODT excipients to mask the taste; thus, neglecting the after taste caused by the unrequired presence of free DS and their threshold of bitter taste in saliva (Sona and Muthulinga, 2011).

The most commonly used superdisintegrants (CP or CCS) were mixed with pellets and tested at concentrations of 2.5, 5, and 10% w/w. For the lubricant with the least metallic taste and good mouthfeel, we added NSF instead of the commonly used magnesium stearate (Shiyosaku et al., 1999). Other excipients that were precisely selected include microcrystalline cellulose pH 101 (MCC) as compressible vehicle, CSD as glidant and mannitol as tablet filler for the pleasant taste.

Angle of repose, compressibility index, and Hausner ratio have been widely used to evaluate powder flowability. Flowability is considered an essential property of powder and powder blends owing to its great impact on many pharmaceutical processes such as blending, compression and handling. The powder flow and compressibility properties were therefore measured for the formulations. The angle of repose for the powder blends was within the range, 28.4 ± 0.55–33.12 ± 0.12. These values represented a good flow property for the powder blends of all formulations according

to the USP. The values for the compressibility index (Carr's index) and Hausner ratio were 11.7–19.7 and 1.04 ± 0.05–1.23 ± 0.11, respectively, and are indicators of good to fair compressibility according to USP. The achieved acceptable flow properties contributed to the shape and surface properties of pellets as well as the low moisture content (≤2%) maintained during pellet preparation.

The pellet formulations of single coat and double coat blends and the test excipients were directly compressed into tablets. Table 3 shows the average values for tablet weights, hardness, tablet thickness, friability and drug content. The values for hardness ranged from 3.43 ± 0.04 to 3.75 ± 0.09 kg, considering that tablet formulations must show good mechanical strength with sufficient hardness to withstand shipping, packaging, and handling. Friability results showed values ≤1%, which is the limit stated by the USP test. Friability values for all formulations were within the range, 0.295 ± 0.20–0.355 ± 0.3%. Based on the above results, sufficient mechanical integrity and strength were achieved for the prepared tablets according to the USP requirements.

As shown in Table 3, all formulated tablets passed the weight variation test. The results obtained from this test were found to be within the acceptable ± 10% limit according to BP. The produced tablets had an average thickness ranging from 2.54 mm ± 0.03 to 2.76 mm ± 0.03, depending on the bulk density of the added ingredients. The DS contents of ODTs were within the acceptable limit of ±5% as stated in USP and were later within the range, 99.4 ± 2.12–101.1 ± 0.99%.

3.6. In vitro disintegration time for DS ODTs

The disintegration time for the ODTs is considered a key feature in their design. Acceptable ODTs should rapidly disintegrate in the mouth within 60 s according to USP. The disintegration time was derived by placing the ODT in SSF to mimic mouth conditions. Disintegration time is mainly controlled using a suitable superdisintegrant. All formulations showed a disintegration time less than 45 s. Comparatively, the disintegration times of tablets were in favor of CP rather than CCS. The faster disintegration of tablets with 10% CP (25 s) may be attributed to its high cross-linking density and rapid capillary activity, which may allow the tablets to swell rapidly as described by Pandey et al. (2003) and Zhang et al. (2010). CCS, on the other hand, is more soluble than CP and has less cross-linking density and more water absorption.

3.7. In vitro release of DS from ODTs

The *in vitro* release of DS from ODTs for F10, F11, and F12 was tested in 0.1 M Hcl (pH 1.2) for 2 h followed by a test of the release in phosphate buffer (pH 6.8) for an additional 2 h to mimic *in vivo* release in GIT. The % DS release in HCl was in the range, 2.75–4.57% for tablets with a 12% enteric coat; tablets for the double-coated pellets showed DS release in the range, 2.5–3.5%. These results indicate a successful enteric coating in formulated ODTs tablet with the product adhering to USP requirements where less than 10% of drug is released from enteric-coated products after the first 2 h in an acidic medium (Mohan et al., 2016). It was also observed that DS release from tablets was almost completed within 2 h after a pH change to 6.8.

3.8. Comparison of DS release from selected ODT formulation to the marketed enteric-coated DS tablets (Voltaren® 25 mg)

From the results of the ODTs release study, formulation F12, which contained the highest CP %, fastest DS release and least release at acidic pH, was selected and compared to the commercially available Voltaren® 25 mg. As shown in Fig. 3, both formulations showed limited DS release in 0.1 N HCl and did not exceed 3% in 2 h. This indicated an efficient enteric coating effect for the coated pellets and the marketed product as they retarded DS release at pH 1.2. Furthermore, the release rate of DS from the selected ODT formulation (F12) at pH 6.8 was significantly higher than that of the marketed product. This may be due to the fast disintegration (tablet to pellets) that results from the high surface area compared to the slow disintegration that occurs with the commercial tablet. The extent of DS release from the two formulations was almost the same that was about 100% after 2 h at pH 6.8. However, the faster drug release from the F12 ODT formulation indicates its superiority over the commercial tablet as a shorter onset of drug action is expected which is required for efficient pain relief. This is an added feature to the expected patient compliance and the no water requirements when taking the proposed superior tablet.

3.9. In vivo disintegration and taste evaluation

ODTs allow drugs to be in contact with the taste buds of patients as they disintegrate or are dispersed in the buccal cavity. Thus, taste masking is crucial in enhancing palatability and improving patient compliance when taking these dosage forms. The taste masking of bitter active substances such as DS is essential to the successful development of ODT formulations. In addition to taste, mouthfeel, the after taste and general acceptability are very important features to consider when developing and formulating ODTs.

We designed two tablet formulations, F12 (formula A), which contained double-coated pellets (coated with taste mask and

Table 3
Physical evaluation of ODTs prepared from 12% Eudragit L100 coated pellets and double coated pellets of 12% Eudragit L100 and 5% Eudragit E 100 (mean ± SD).

Formulation Code	Weight (mg)	thickness (mm)	Hardness (kg)	Friability (%)	Drugs Content (%)
12% Eudragit L 100 coated pellets					
F1	200.16 ± 1.56	2.60 ± 0.02	3.43 ± 0.06	0.353 ± 0.21	101.10 ± 0.99
F2	199.93 ± 2.38	2.76 ± 0.03	3.52 ± 0.02	0.295 ± 0.20	99.40 ± 2.12
F3	199.63 ± 1.44	2.73 ± 0.02	3.43 ± 0.05	0.332 ± 0.09	99.67 ± 1.98
F4	199.70 ± 1.20	2.54 ± 0.03	3.75 ± 0.09	0.355 ± 0.07	99.52 ± 1.24
F5	199.45 ± 2.32	2.64 ± 0.02	3.63 ± 0.05	0.313 ± 0.12	99.51 ± 2.11
F6	200.16 ± 1.56	2.60 ± 0.02	3.43 ± 0.06	0.353 ± 0.20	101.10 ± 0.99
Doubled coated pellets[*]					
F7	199.93 ± 2.38	2.76 ± 0.03	3.52 ± 0.02	0.295 ± 0.12	99.40 ± 2.12
F8	199.63 ± 1.44	2.73 ± 0.02	3.43 ± 0.05	0.332 ± 0.20	99.67 ± 1.98
F9	199.7 ± 1.20	2.54 ± 0.03	3.75 ± 0.09	0.355 ± 0.3	99.52 ± 1.24
F10	199.45 ± 2.32	2.64 ± 0.02	3.63 ± 0.05	0.313 ± 0.09	99.51 ± 2.11
F11	200.16 ± 1.56	2.60 ± 0.02	3.43 ± 0.06	0.353 ± 0.11	101.10 ± 0.99
F12	199.93 ± 2.38	2.76 ± 0.03	3.52 ± 0.02	0.295 ± 0.14	99.40 ± 2.12

[*] Double coated pellets of 12% Eudragit L100 coat followed by 5% Eudragit E 100 coat.

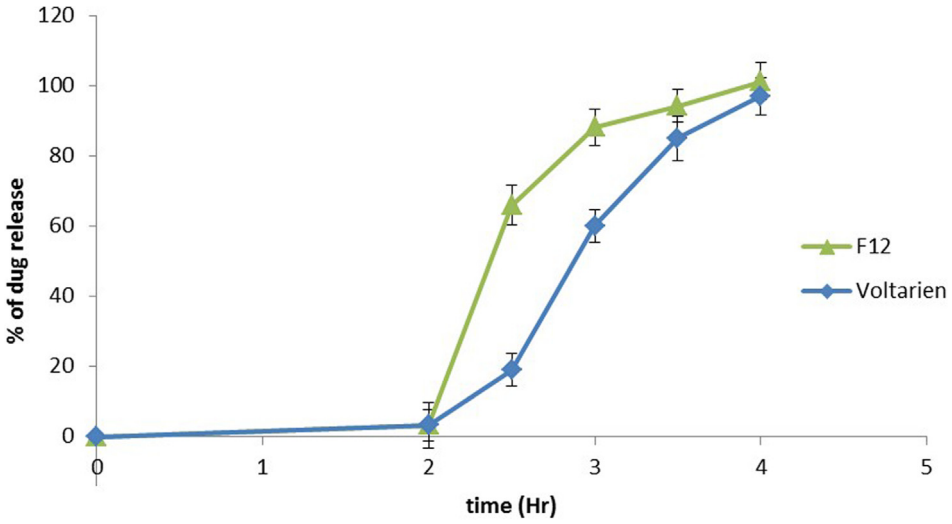

Fig. 3. In-vitro release of DS from Voltaren® 25 mg tablets compare with optimized ODT formula F12.

enteric coating polymers) and F6 (formula B), which contained only enteric-coated pellets, and tested their effectiveness using 10 volunteers. Formula B was included in the study to determine whether enteric coating would be sufficient to mask the taste of DS in the presence of pleasant-tasting excipients such as mannitol and the superdisintegrant, CP. Mannitol (a sugar-based excipient) and other soluble excipients were selected to improve the palatability of the tablets; mannitol in particular, was selected for its cool, sweet and mild taste and as it is expected to provide a pleasant mouth feel due to its negative heat of solution (Rowe et al., 2009). The results of the taste evaluation for each volunteer are summarized as overall average points in Table 4.

From the above results, it was clear that the ODT of formula A (where DS pellets were coated with a taste masking polymer, Eudragit E 100) following an initial enteric coating (Eudragit L 100)) lacked a bitter taste with high acceptability. However, formula B having the enteric coat only was less acceptable than formula A, and had an assured after taste as drug release in the saliva was not completely prevented. This indicated that good tasting excipients such as mannitol and superdisintegrant decrease the bitter taste for 3 min, and is followed by a strong bitter after taste (score 4).

Using the paired *t*-test, we found a t value of 3.6, which indicated significant difference between treatments A and B ($P < 0.05$). Treatment A was superior to treatment B in over all acceptability and indicated that the bitter taste required coating of the drug with a pH-dependent polymer such as Eudragit E100 that is insoluble in saliva (pH 6.8).

Table 4
Feedback of volunteers about disintegration time in mouth, mouth feeling, taste upon disintegration and after taste of DS ODTs of treatment A and B.

Formula A: double coated pellets designated as ★

Formula B: 12 % coated pellets designated as ●

Volunteer Initials	Disintegration time[a] (s)		Bitterness[b]				Mouth feel[c]				After taste				Over all acceptability[d]			
	★	●	Extremely bitterness Not at all				Very grittiness Very creamy				Very Bitterness Not at all							
			1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
H.A	15	17	★●				★●				★			●		★		●
D.S	13	15	★●					★●				★		●		★		●
D.J	12	19	★●				●	★			★			●		★		●
Sh.F	15	20	★●				★●					★		●	★			●
S.G	12	20	★	●			★●					★		●		★		●
S.F	14	15	★●					★●				★		●		★	●	
A.A	15	17	★●				★●				★			●		★		●
S.A	17	19	★	●			★●				★			●		★	●	
F.B	14	18	★●				★●				★			●		★		●
H.A	15	15	★●				★●				★			●		★		●
Average	★ 14.2 ± 1.5				1 ± 0				1.3 ± 0.5				1.4 ± 0.52				1.9 ± 0.3	
	● 17 ± 2				1.2 ± 0.4				1.2 ± 0.4				4 ± 0				3.8 ± 0.42	

[a] Disintegration time is the time for the tablets to be broken into fine particles.
[b] Bitterness: 1 = not at all bitter; 2 = slightly bitter, 3 = highly bitter; 4 = extremely bitterness.
[c] Mouth feel: 1 = very creamy; 2 = creamy; 3 = gritty; 4 = very gritty.
[d] Overall acceptability 1 = very good; 2 = good, 3 = acceptable; 4 = not acceptable.

4. Conclusion

Orally disintegrating tablets of DS was designed to be fast disintegrated in mouth into macro smooth double coated pellets. The pellets were prepared by layering DS onto sugar spheres followed by enteric coat (Eudragit L 100) and then a taste masking coat (Eudragit E 100). Fluidized bed technology was utilized in the production of the coated pellets. The quality of the obtained coat (enteric and taste masking) was optimized during the processing. The coated pellets were formulated into ODTs with the property of fast disintegration in mouth and DS to be released only in intestine. The designed tablets could be just administered without water to be disintegrated in the mouth with palatable taste and expected good patient compliances. The designed tablets will be safe and not irritating to stomach with fast release of DS from the pellets in intestine. All obtained results showed high quality ODT with the desired unique properties.

Conflict of interest

The authors declare that they have no conflict of interest.

References

Abdelbary, A., Elshafeey, A.H., Zidan, G., 2009. Comparative effects of different cellulosic-based directly compressed orodispersable tablets on oral bioavailability of famotidine. Carbohydr. Polym. 77, 799–806.

Aguilar-de-Leyva, A., Sharkawi, T., Bataille, B., Baylac, G., Caraballo, I., 2011. Release behaviour of clozapine matrix pellets based on percolation theory. Int. J. Pharm. 404, 133–141.

Al-Omran, M.F., Al-Suwayeh, S.A., El-Helw, A.M., Saleh, S.I., 2002. Taste masking of diclofenac sodium using microencapsulation. J. Microencapsul. 19, 45–52.

Bandari, S., Mittapalli, R.K., Gannu, R., Rao, Y.M., 2008. Orodispersible tablets: an overview. Asian J. Pharm. 2, 2–11.

Bhasin, R.K., Bhasin, N., Ghosh, P.K., 2011. Advances in formulation of orally disintegrating dosage forms: a review article. IGJPS 4, 328–353.

Biju, S.S., Saisivam, S., Maria, N.S., Rajan, G., Mishra, P.R., 2004. Dual coated erodible microcapsules for modified release of diclofenac sodium. Eur. J. Pharm. Biopharm. 58, 61–67.

Bott, C., Rudolph, M.W., Schneider, A.R.J., Schirrmacher, S., Skalsky, B., Petereit, H.U., Langguth, P., Dressman, J.B., Stein, J., 2004. In vivo evaluation of a novel pH- and time-based multiunit colonic drug delivery system. Aliment Pharmacol. Ther. 20, 347–353.

Chang, R.-K., Hsiao, C., 1989. Eudragit RL and RS pseudolatices: properties and performance in pharmaceutical coating as a controlled release membrane for theophylline pellets. Drug Dev. Ind. Pharm. 15, 187–196.

Chang, R.K., Peng, Y., Trivedi, N., Shukla, A.J., 2009. Polymethacrylates. In: Rowe, R.C., Sheskey, P.J., Quinn, M.E. (Eds.), Handbook of Pharmaceutical Excipients. sixth ed. Pharmaceutical Press, American Pharmaceutical Association, London, Chicago, pp. 525–533.

Chatlapalli, R., Rohera, B.D., 1998. Physical characterization of HPMC and HEC and investigation of their use as palletization aid. I.J.P. 161, 179–193.

Ciper, M., Bodmeier, R., 2005. Preparation and characterization of novel fast disintegrating capsules (fastcaps) for administration in the oral cavity. Int. J. Pharm. 303, 62–71.

Dastidar, S.G., Ganguly, K., Chaudhuri, K., Chakrabarty, A.N., 2000. The antibacterial action of diclofenac shown by inhibition of DNA synthesis. Int. J. Antimicrob. Agents 14, 249–251.

Dyankova, S., Doneva, M., Todorov, Y., Terziyska, M., 2016. Determination of particle size distribution and analysis of a natural food supplement on pectin base. IOSR J. Pharm. 6, 1–8.

Evonik, 2009. Eudragit Application Guide. Evonik Röhm GmbH, Darmstadt, Germany.

FDA, 2008. Guidance for Industry: Orally Disintegrating Tablets. Center for Drug Evaluation and Research, pp. 1–6.

Gohel, M., Patel, M., Amin, A., Agrawal, R., Dave, R., Bariya, N., 2004. Formulation design and optimization of mouth dissolve tablet of nimesulide using vacuum drying technique. AAPS Pharm. Sci. Tech. 5 (3), 10–15.

Han, X., Wang, L., Sun, Y., Liu, X., Liu, W., Du, Y., Li, L., Sun, J., 2013. Preparation and evaluation of sustained-release diltiazem hydrochloride pellets. Asian J. Pharm. Sci. 8 (4), 244–251.

Ibrahim, M.A., 2013. Formulation and evaluation of mefenamic acid sustained release matrix pellets. Acta Pharm. 63, 85–98.

Jones, D., 1994. Air suspension coating for multiparticulates. Drug Dev. Ind. Pharm. 20, 3175–3206.

Joshi, Meenakshi, 2013. Role of Eudragit in targeted drug delivery. Int. J. Curr. Pharm. Res. 5, 58–62.

Kumari, M.H., Samatha, J., Balaji, A., Shankar, U., 2013. Recent novel advancements in pellet formulation review. Int. J. Pharm. Sci. Res. 4 (10), 3803–3822.

Leopold, C.S., Eikeler, D., 1998. Eudragit E as coating material for the pH-controlled drug release in the topical treatment of inflammatory bowel disease (IBD). J. Drug Target. 6 (2), 85–94.

Ma, J., Hadzija, B., 2013. Basic Physical Pharmacy. Jones & Bartlett Learning, Burlington, MA, pp. 240–259.

Mohan, S.D., Gupta, V.R.M., Manaswini, Y., 2016. Impact of over coat application on enteric coated drug pellets: design to protect from stomach environment. Int. Res. J. Pharm. 7 (10), 14–18.

Mehta, Mohit, Bhagwat, Deepak P., Gupta, G.D., 2009. Fast dissolving tablets of sertraline hydrochloride. IJCRGG 1, 925–930.

Pahwa, R., Piplani, M., Sharma, P.C., Kaushik, D., Nanda, S., 2010. Orally disintegrating tablets Friendly to pediatrics and geriatrics. Arch Appl Sci Res. 2, 35–48.

Pandey, S., Shenoy, V., Agarwal, S., Gupta, R., 2003. Optimizing fast dissolving dosage form of diclofenac sodium by rapidly disintegrating agents. Ind. J. Pharm. Sci. 23, 197–201.

Pearnchob, N., Bodmeier, R., 2003. Dry polymer powder coating and comparison with conventional liquid-based coatings for Eudragit(R) RS, ethylcellulose and shellac. Eur. J. Pharm. Biopharm. 56, 363–369.

Pfister, W., Ghosh, T., 2005. Orally disintegrating tablets: product, technologies, and development. Pharm. Tech. 29, 136.

Rahman, Md.A., Ali, J., 2008. Development and in vitro evaluation of enteric coated multiparticulate system for resistant Tuberculosis. Indian J. Pharm. Sci. 70 (4), 477–481.

Rowe, R.C., Sheskey, P.J., Quinn, M.E. (Eds.), 2009. Handbook of Pharmaceutical Excipients. sixth ed. Pharmaceutical Press, American Pharmaceutical Association, London, Chicago, p. 525.

Sastry, S.V., Nyshadham, J.R., Fix, J.A., 2000. Recent technological advances in oral drug delivery. A review. Pharm. Sci. Technol. Today 4, 138–145.

Senthil Kumar, K.L., Ashokkumar, S., Ezhilmuthu, R.P., 2010. Formulation and evaluation of didanosine enteric coated sustained release tablet. J. Biomed Sci and Res. 2 (3), 126–131.

Shiyosaku, K., Kiyo, M., Kazumi, T., 1999. Quickly disintegrable solid preparations. JP 11130662, Japan.

Singh, S., Neelam Arora, S., Singla, Y.P., 2015. An overview of multifaceted significance of eudragit polymers in drug delivery systems. Asian J. Pharm. Clin. Res. 8 (5), 1–6.

Sona, P.S., Muthulinga, C., 2011. Formulation and evaluation of taste masked orally disitegrating tablets of diclofenac sodium. Int. J. Pharmtech. Res. 3, 819–826.

Srivastava, S., Mishra, G., 2010. Fluid bed technology: overview and parameters for process selection. IJPSDR 2, 236–246.

Suresh, B., Kumar, M., Ramesh, G., Madhusudan, R., 2008. Orodispersible tablets: an overview. Asian J. Pharm. 2, 2–11.

United States Pharmacopeia and National Formulary USP 32 [USP32NF27, 2010].

Wong, P.M., Chan, L.W., Heng, P.W.S., 2013. Investigation on side-spray fluidized bed granulation with swirling airflow. AAPS Pharm. Sci. Tech. 14 (1), 211–221.

Zhang, Y., Wrzesinski, A., Moses, M., Bertrand, H., 2010. Comparison of superdisintegrants in orally disintegrating tablets. Pharm. Tech. 34 (7), 54–65.