

Preparation, Characterization and Pharmacokinetic Evaluation of Novel Maltodextrin-Based Orally Disintegrating Tablets of Flurbiprofen, Diclofenac Sodium and Pioglitazone Hydrochloride

¹Muhammad Akhlaq, ²Heba F. Mansour and ²Hamdy Abdelkader

¹Department of Pharmaceutics, Faculty of Pharmacy, Gomal University, Pakistan

²Department of Pharmaceutics, Faculty of Pharmacy, Minia University, Egypt

ABSTRACT

Background and Objective: Maltodextrin was investigated as a novel excipient for preparation of Orally Disintegrated Tablets (ODT) of Flurbiprofen (FLB), Diclofenac Sodium (DCL) or Pioglitazone HCl (PGL). **Methods:** A simple preparation technique, wet granulation method was used. The prepared ODT were physically characterized for mechanical properties. *In-vitro* and *in-vivo* disintegration time and drug release as well as accelerated stability have also been investigated. **Results:** The recorded hardness and friability were approximately 4 kg and less than 1% respectively. The prepared ODT revealed very fast *in vitro* and *in-vivo* disintegration and drug release. A good correlation ($R^2 = 0.986$) between *in vitro* and *in-vivo* disintegration time was obtained. The prepared tablets exhibited significantly higher plasma maximum concentration (C_{max}) and lower time for C_{max} (T_{max}) compared to the commercial tablets. Further, the accelerated stability studies indicated that the ODT have good mechanical and physical properties. **Conclusion:** This report warrants maltodextrin as a potential and reliable candidate for preparation of ODT.

Key words: Maltodextrin, hardness, wet granulation, friability and dissolution

Pharmacologia 6 (4): 141-148, 2015

INTRODUCTION

Immediate-release tablets are those which release their drug contents rapidly after administration; these tablets are commonly and widely used by patients due to simplicity, good patient acceptability as well as technicality. They can be manufactured by well-studied techniques and readily available machinery in pharmaceutical plants. Immediate-release tablets can be classified into disintegrating and non-disintegrating tablets (chewable tablets, effervescent tablets and lozenges)¹.

The most common type of disintegrating tablets is that intended to be swallowed and releases its drug content within a short period of time after being disintegrated. In an attempt to develop drug products, there has been recently growing interest in formulation of Orally Disintegrating Tablets (ODT) which disintegrate or dissolve immediately upon being on the tongue². Thus, these formulations can tackle potential issues of patient compliance for certain therapeutic indications and special patient populations.

According to USP, ODT have the convenience of rapidly disintegrating or dissolving within less than 30 sec when contact saliva without the aid of liquid or chewing. Furthermore, ODT can benefit many special patient populations who might experience some difficulties during swallowing such as pediatric, geriatric, nauseated, psychiatric and bed-ridden patients².

Recently, there has been a growing body of research to study different techniques and excipients needed for preparation of ODT^{3,4}. Sugar excipients have been classified into two types; type 1 and type 2. Type 1 includes mannitol, xylitol, lactose and erythritol and exhibits low compressibility. On the other hand, type 2 including maltose and trehalose exhibits high compressibility⁵. Sugar-based ODT require tablet conditioning in order to get a short disintegration time without compromising mechanical properties (hardness and friability) of the tablets. The concept of tablet conditioning involves exposure of ODT to specific conditions of temperature and humidity during which certain physicochemical changes in the internal structures of the formulation take place. These changes lead to improvement of both the mechanical properties and the unique physical characteristic of the fast

Corresponding Author: Hamdy Abdelkader, Department of Pharmaceutics, Faculty of Pharmacy, Minia University, Minia, Egypt

disintegration. For example, spray-drying is a mandatory step during preparation of sugar-based ODT in order to attain the amorphous forms of sugars⁵. These techniques are time consuming and add up value on the final cost of ODT compared with other immediate release tablet formulations. Alternatively, Maltodextrin, an amorphous polysaccharide has been recently used to formulate ODT adopting the wet-granulation technique without the need of the precondition process. This type of ODT has been reported to have fast disintegration with satisfactory mechanical properties³.

Fast disintegrating tablets can be also prepared by molding or compression techniques using wet powders including drugs. Upon drying of such wet masses, tablets of desirable porosity have been generated allowing rapid disintegration in the oral cavity⁶. Nevertheless, molded or wet compressed tablets are formulated empirically and not easily optimized. Therefore, this study aims to utilizing maltodextrin and adopting simple wet-granulation techniques to generate granules of high porosity that can be compressed into ODT. Three model drugs were employed including flurbiprofen and diclofenac sodium as analgesics and pioglitazone as anti-diabetic. These potential candidate drugs are widely used for treatment of chronic diseases such osteoarthritis and diabetes mellitus affecting elderly patients. The current study is novel and unique in the sense that deriving insight from the exciting research findings and advancements in the field of pharmaceutical sciences has been made to enhance its practical utility and market impact throughout the globe.

MATERIALS AND METHODS

Materials: Flurbiprofen, Diclofenac Sodium and Pioglitazone HCl were kindly supplied by Wilshire Pharmaceuticals (Lahore, Pakistan), Hilton Pharmaceuticals (Karachi, Pakistan) and Abbot Laboratories (Karachi, Pakistan) respectively. Crosscarmilose Sodium, maltodextrin, mannitol, aerosil and talc were gifted from Global Pharmaceuticals, Islamabad. All the chemicals were of analytical grade and were used without further purification.

Methodical investigation: A UV/Visible double beam spectrophotometer (Shimadzu, 1601, Japan) was used for construction of the calibration curve and *in-vitro* dissolution studies. Drug concentration range of 5-50 $\mu\text{g mL}^{-1}$ was employed for construction of calibration curves.

A simple, rapid and simultaneous HPLC method was developed for determination of FLB, DCL and PGL concentration in plasma. An HPLC system

(Agilent 1200, Agilent Corporation, Germany) comprising a quaternary pump, an automatic sampler and a Photodiode Array (PDA) detector was used with data acquisition by ChemStation[®] software (Agilent Corporation, Germany). Calibration curves were constructed using the same concentration range mentioned above. Mean percent recovery, inter and intraday reproducibility studies were carried out.

Evaluation of starting materials:

Solubility study: Solubility of pure FLB, DCL and PGL was studied in aqueous solutions of different pH values⁷. Excess amount of each drug was added separately to seven different solutions including 0.1 N HCL (pH 1.2), phosphate buffer solutions (pH 6.8, 7.2, 7.4), 0.1 N NaOH (pH 10), distilled water and hydroalcoholic solution in stoppard flasks. Flasks were maintained at three different temperatures (25 ± 2 , 37 ± 2 and $40 \pm 2^\circ\text{C}$) and shaken thermostatically for 24 h using shaking water bath (Shel lab, USA). The resultant mixtures were allowed to equilibrate for further 24 h, centrifuged for 10 min at 3000 rpm and filtered through filter membranes of pore size 0.45 μm . The filtrates were analyzed after appropriate dilutions and the drug contents were determined spectrophotometrically by measurement at 247, 276 and 265.5 nm for DCL, PGL and FLB, respectively.

Differential Scanning Calorimetry (DSC): The physicochemical compatibility of FLB, DCL, PGL and the used excipients were investigated by Differential Scanning Calorimetric (DSC) analysis, using a DSC-50 (Shimadzu, Japan) calibrated with an indium standard. About 5-10 mg of the samples were weighed in aluminium standard crucible pans (40 μL), sealed with pierced lids and heated at a constant rate of $10^\circ\text{C min}^{-1}$ over a temperature range of 50-400 $^\circ\text{C}$ under a purge of nitrogen gas.

Physical properties of unprocessed drug powders:

Powder flowability, particle size, density, compressibility and water absorption capacity were investigated. Powder flowability was determined through measuring the angle of repose adopting the cone method. Particle size was measured using series of sieves. Bulk and tapped densities were determined by a cylinder method⁸ whereas the bulk density was the density after 3 min tapping (60 taps/min). Based on the angle of repose results, the powders were agitated for 20 min to achieve the uniform distribution before compression. Compressibility, C, was calculated as follows:

Table 1: Composition of the prepared orally disintegrating tablets ODT

Formulation	Drug	Mannitol	Maltodextrin	Crosscarmillose	Talc	Aerosil	Total
DCL-MLT	50	302.5	100	40	5	2.5	500
PGL-MLT	15	337.5	100	40	5	2.5	500
FLB-MLT	50	302.5	100	40	5	2.5	500

All quantities were taken in milligrams

$$C (\%) = 100 (D-L)/D \quad (1)$$

where, 'D' and 'L' denote tapped and bulk densities, respectively. The true density was measured with a Helium-Air Pycnometer (Model-1305, Micromeritics, USA).

Preparation of ODT formulations: Three ODT formulations, each weighing 500 mg, were prepared using wet granulation method by modifying the method described by Sunada and Bi⁶. Tablet composition is shown in Table 1. In brief, kneading was performed in a multi-purpose powder handling mill (MECHANOMILL Okada Seiko, Co. Ltd. Tokyo, Japan) with a fixed paddle rotation speed of 2500 rpm.

Distilled water was added to 50 g of the powder mix (except the lubricant) and then the powder was agitated for 60 sec. The wet powder mass was then extruded through a sieve number 120 into a container and covered with a wet paper towel. Wet granules were dried in a circulating-air at 60°C for 3 h. Prior to compression, appropriate amount of lubricant was added to the granules and then mixed gently with a spatula. Finally, the dried granules were compressed into flat-faced tablets 11 mm in diameter and 4.8 mm in thickness using a single punch machine (Erweka, Germany). Tablets with a dry weight of 500 mg were kept at room temperature in an air-tight container for further investigations.

Evaluation of prepared ODT formulations

Hardness and friability studies: Hardness is the force required to break a flat-faced tablet into halves by compression in the radial direction. Hardness of the different tablet formulations was recorded using a tablet hardness tester (TS-50N, Okada Seiko, Japan) with the plunger driven down at a speed of 20 mm min⁻¹.

For friability testing, 10 tablets from each formulation were accurately weighed, placed in a friabilator (Erweka, Germany) and rotated for 4 min (100 rotations). Tablets were reweighed and the friability was calculated according to the following equation⁸. The mean of three Measurements ± SD was estimated.

$$\text{Friability} = \frac{W_1 - W_2}{W_1} \times 100 \quad (2)$$

where, W₁ is the initial weight and W₂ is the final weight of the tablets.

Thickness, diameter and weight variation measurements: The thickness and diameter of the tablets were determined by using Vernier Caliper, India, data presented in Millimeters ± Standard Deviation SD.

Wetting time and water absorption ratio: A piece of paper tissue (15 × 15 mm) was folded twice and placed in a Petri dish containing 6 mL of water. A tablet was put on the paper and the time for complete wetting was measured. The wetted tablet was then weighed and water absorption ratio, R was determined according to the following Eq. 3:

$$R = 100 (W_a - W_b)/W_b \quad (3)$$

where, W_b and W_a are the weight before and after water absorption, respectively.

In-vitro release studies: In-vitro release study was performed on the ODT formulations according to USP apparatus 1, using 8-station dissolution apparatus, Pharma Test Model #PTWS-11/P, TPT (Hunburg, Germany). Each flask was filled with 900 mL dissolution medium (0.2M phosphate buffer solution, pH 7.4) maintained at 37 ± 0.1°C and stirred at 100 rpm (Perfect sink conditions). Samples were collected manually and replaced with an equivalent volume of fresh dissolution media. After filtration through a 0.22 μm membrane, drug concentration was determined spectrophotometrically by measurement of UV absorbance at 247, 276 and 265.5 nm for FLB, DCL and PGL, respectively. All the study was carried out in triplicate.

Oral disintegration studies: Oral disintegration study was conducted in six healthy volunteers who randomly administered three kinds of tablets at 24 h intervals at their desire. The time required for complete disintegration of each formulation in the oral cavity was collected.

In-vivo animal study conditions: The study was carried out according to Laboratory Animal Care Principles and was approved by Ethical Committee, Faculty of Pharmacy, Gomal University, D.I.Khan. Thirty six healthy male Albino rabbits weighing 3.0 kg each were housed under standard conditions with free access to water and food. Before each study, the rabbits were fasted overnight. Food was given freely to the rabbits 2 h after dosing. The rabbits were randomly divided into three groups, each comprising 12 rabbits. Each group was subdivided into two groups of six rabbits each. Three sub groups were administered the commercial tablets of FLB, DCL and PGL containing 50, 50 and 15 mg active drug powder, respectively whereas the other three sub groups received corresponding ODT formulations. Rabbits were placed in a body-restraint during administration of the tablet formulations. The tablets were placed in the rabbit's mouth and wetted with about 2 mL of water. Gentle tension was applied by the operator to restrain the rabbit's mouth for 1 min in order to avoid chewing and ensure complete disintegration of the ODT formulations. For the other three sub groups of rabbits, the commercial tablets were placed deeper in the mouth with about 2 mL of water to facilitate swallowing. After dosing, 2.6 mL blood samples were withdrawn from the marginal ear vein into pre-labelled heparin beaded tubes at time points 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 18 and 24 h. Blood samples were centrifuged at 3000 rpm at 4°C for 15 min within 1 h of the sample collection time. The resultant plasma was separated from the centrifuged samples and frozen at -10°C until subsequent analysis.

Chromatographic Analysis of FLB, DCL and PGL by HPLC: Plasma samples were defrosted and equilibrated to room temperature. About 10 μ L of DCL, PGL or FLB solutions (internal standards, 8 μ g mL⁻¹) was added to 0.1 mL of plasma and 1 mL of ether. The mixtures were vortexed for 2 min and centrifuged at 4,000 rpm for 15 min to precipitate proteins. The supernatant was transferred to separate test tubes and evaporated till dryness using a water bath adjusted at 40°C. The residue was reconstituted in 100 μ L of the mobile phase, vortexed for 2 min and then injected into the HPLC system.

The HPLC analysis method is a modification of that described by Akhlaq *et al.*⁹ An HPLC system (Agilent 1200, Agilent Corporation, Germany) comprising a quaternary pump, an automatic sampler and a photodiode array (PDA) detector was used with data acquisition by ChemStation[®] software

(Agilent Corporation, Germany). The chromatographic separation was achieved using a Gemini C18 column (5 μ m, 4.6 mm \times 250 mm, Phenomenex, California, USA) maintained at 25°C. The adopted mobile phase was 50:50 v/v disodium hydrogen phosphate solution (30 mM, pH 7.0) and acetonitrile. The isocratic flow rate was 1.0 mL min⁻¹. A mixture of acetonitrile and water (50:50 v/v) was used as a rinse solution for the injector. The injection volume was fixed at 5 μ L. Detection was carried out using a wavelengths of 247, 276 and 265.5 nm for FLB, DCL and PGL respectively. The peak purity for FLB, DCL and PGL was also determined.

Pharmacokinetics and statistics: Pharmacokinetic parameters, such as Area Under the Curve (AUC), peak concentration (C_{max}), Time to attain peak concentration (T_{max}) and Elimination half-lives ($t_{1/2}$) were derived from the plasma concentration versus time data using. A non-compartmental approach implemented in Kinetica version 5.0 was used for computing the above pharmacokinetic parameters. The values of the elimination rate constant (k_{el}) were used to calculate the absorbed and unabsorbed fractions of drugs using Wegnar-Nelson method given in Pk-Fit version 2.01. All data are expressed as Mean \pm Standard Deviation (SD). The differences in the average of data were compared by simple analysis of variance using the software SPSS Statistics (Version 17.0, Chicago, USA), in which $p < 0.05$ was considered to be significant.

Accelerated stability studies: The effect of aging on drug release from the prepared ODT formulations of FLB, DCL and PGL was investigated according to International Commission for Harmonization (ICH) guidelines. The tablet formulations were placed in amber bottles and stored in a stability chamber at 40°C and Relative Humidity (RH) of 75 \pm 5% for a period of 4 weeks. The stored samples were tested for mechanical properties (friability and hardness) and *in-vitro* and *in-vivo* disintegration.

RESULTS

Methodical investigation: Analytical technique might prove that the three drugs showed the best linearity in phosphate buffer solution (pH 7.4) over the concentration range of 5-50 μ g mL⁻¹ with a correlation coefficient of 0.999.

HPLC calibration curves for FLB, DCL and PGL were linear ($r \geq 0.9996$, 0.999 and 0.9992, respectively) over the concentration range of 5-50 μ g mL⁻¹. Mean percentage recovery \pm percentage Relative Standard

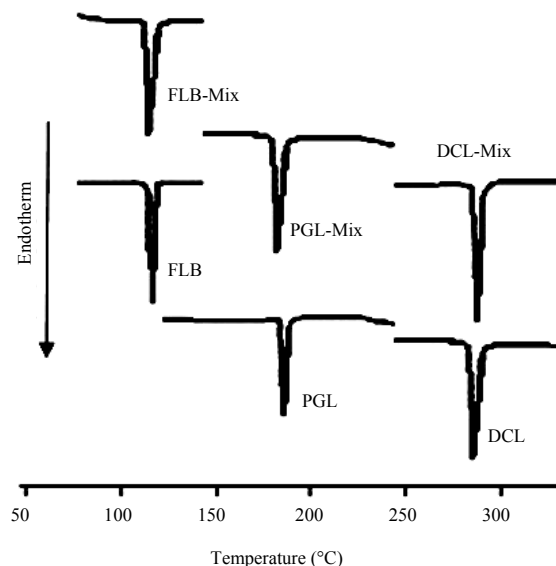


Fig. 1: DSC Thermograms of DCL, PGL and FLB unprocessed powders and their corresponding physical mixtures
 FLB: Flurbiprofen, DCL: Diclofenac Sodium, PGL: Pioglitazone HCL

Table 2: Aqueous solubility of unprocessed FLB, PGL and DCL

Drugs	pK _a	Solubility at pH 1.2-10 at 25, 37 and 40°C (mg mL ⁻¹)	Solubility at pH 7.4 at 37°C (mg mL ⁻¹)
DCL	3.99±0.01	0.005±0.18 to 12.23±1.01	12.230±1.01
PGL	5.60±0.03	1.393±0.02 to 8.221±0.11	7.700±0.07
FLB	4.22±0.03	1.474±0.04 to 6.961±0.13	6.661±0.09

Table 3: Physical properties of the starting materials

Evaluation of starting materials	DCL	PGL	FLB
Particle size range (μm)	54.03-98.34	50.24-80.14	54.03-98.34
Angle of repose θ (°)	40.63±0.62	29.01±0.43	40.23±0.32
Compressibility index (%)	33.40±1.00	36.21±0.72	34.23±1.05
True density (g cm ⁻³)	1.30±0.06	1.02±0.03	1.33±0.26
Loose bulk density (g cm ⁻³)	0.31±0.03	0.35±0.11	0.30±0.73
Dense bulk density (g cm ⁻³)	0.53±0.11	0.55±0.10	0.52±0.00
Hausner ratio	1.47±0.02	1.49±0.13	1.50±0.20

Experiments were conducted in triplicate and Mean ±SD was tabulated

Deviation (RSD) ranged from 96.99±0.005 to 103.12±0.008. Inter and intra-day reproducibility was also in acceptable range of 98.11±0.001 to 103.56±0.012.

Evaluation of starting materials

Solubility studies: DCL is a salt of weak acid; PGL is a weak acidic drug while FLB is a monoprotic drug. The aqueous solubilities of the three drugs and their pKa values are shown in Table 2.

Differential Scanning Calorimetry (DSC): The DSC thermograms of the unprocessed powders of the

investigated drugs and their corresponding physical mixtures with different excipients are illustrated in Fig. 1. The DSC thermograms of FLB, DCL and PGL unprocessed powder showed sharp melting endothermic peaks at 114, 180 and 280°C, respectively. The thermograms of the physical mixtures showed the same characteristic features of the unprocessed drugs with no change in the corresponding melting temperatures.

Physical properties of starting materials: Table 3 shows the values of particle sizes, angle of repose, compressibility index and water absorption ability of unprocessed drug powders. The range of particles size was 50-98 μm (the lower limit of the sieve range). The angle of repose ranged from 29.01±0.43 to 40.6±0.62. Compressibility index estimated for drug powders were found to be 43.40±1.05 to 36.2±0.72% while the Hausner ratio ranged from 1.47±0.02 to 1.50±0.05. True, bulk and tapped densities ranged from 1.02±0.03 to 1.33±0.26, 0.30±0.73 to 0.35±0.11 and 0.52±0.00 to 0.55±0.10 gm⁻³, respectively.

Table 4: Dimensions and mechanical properties of the prepared ODT

Formulations	Weight variation (%)	Thickness (mm)	Diameter (mm)	Hardness (kg)	Friability (%)
Diclofenac sodium	2.4±0.32	4.8±0.03	11±0.02	3.8±0.72	0.52±0.01
Pioglitazone HCl	2.7±0.11	4.8±0.11	11±0.11	3.5±0.21	0.76±0.17
Flurbiprofen	3.0±0.07	4.8±0.20	11±0.07	3.9±0.07	0.45±0.01

Experiments were conducted in triplicate and Mean±SD was tabulated

Table 5: Water absorption, *in-vitro* and oral disintegration properties of the prepared ODT

Formulation	Water absorption time (Sec)	Water absorption ratio (R)	<i>In vitro</i> disintegration time (Sec)	Oral disintegration time (Sec)
Flurbiprofen	34±0.87	49.21±0.11	50±3.5	44±1.5
Diclofenac Sodium	23±0.12	55.64±0.54	46±2.0	40±2.0
Pioglitazone HCl	30±0.23	63.32±0.02	40±1.5	33±1.0

Experiments were conducted in triplicate and Mean±SD was tabulated

Table 6: Pharmacokinetic parameters of FLB, DCL and PGL after administration of ODT Formulations or their respective commercial tablets to albino rabbits

Formulations	C_{max} ($\mu\text{g mL}^{-1}$)	T_{max} (h)	AUC_{0-8} ($\mu\text{g. h mL}^{-1}$)
Flurbiprofen	976.22±67.34	1.6±0.04	1610.92±12.01
Diclofenac sodium	1022.50±45.32	1.5±0.10	1892.23±20.15
Pioglitazone HCl	998.21±32.33	1.6±0.01	1672.72±33.21
Flurbiprofen commercial [®]	465.11±23.02	2.1±0.02	991.03±18.7
Diclofenac sodium commercial [®]	653.21±15.24	2.1±0.10	1220.01±11.25
Pioglitazone HCL commercial [®]	571.02±25.34	2.0±0.30	1091.25±35.50

Experiments were conducted in triplicate and Mean±SD was tabulated

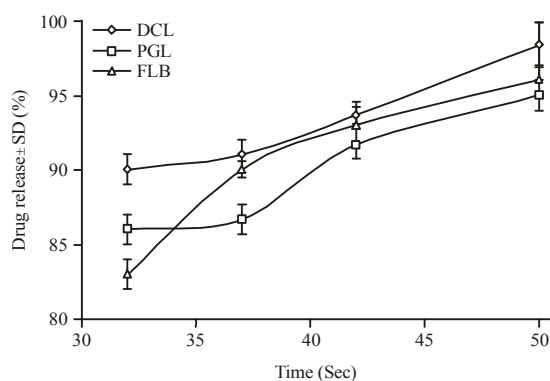


Fig. 2: *In-vitro* release profiles of FLB, PGL and DCL from orally disintegrating tablet. The values were calculated in triplicate

Evaluation of prepared ODT formulations

Hardness and friability studies: Table 4 shows hardness and friability results. Tablets thickness and diameter were constant over the range of 4.8 ± 0.03 to 4.8 ± 0.20 mm and 11 ± 0.02 to 11 ± 0.11 mm, respectively. Hardness of the prepared tablets fell into the range of 3.5 ± 0.21 kg to 3.9 ± 0.07 kg. The friability of the prepared tablets ranged from 0.45 ± 0.01 to $0.76\pm 0.03\%$.

Wetting time, water absorption, disintegration and *in-vitro* release studies: The wetting time, water absorption and *in-vitro* drug release were studied for all the three formulations using a method described by

Sunada and Bi⁶. All formulations had short absorption time, high water absorption ratios and fast *in vitro* and oral disintegration times (Table 5). The percentage of drug release from FLB, DCL and PGL tablets was 96.56, 95.44 and 98.54%, respectively within 50 sec. All the formulations show a great pact of swelling and water absorption and were disintegrated rapidly within the time span of few seconds which is the main feature of this dosage form (Fig. 2).

***In-vivo* animal studies:** Figure 3 and Table 6 show the mean serum concentration-time profiles and the mean pharmacokinetic parameters of FLB, DCL and PGL, respectively after oral administration of the prepared ODT formulations and the corresponding commercial tablets. The values of C_{max} of the prepared tablet formulations were significantly higher than those of the corresponding commercial tablets ($p < 0.05$). Moreover, T_{max} values of the prepared ODT formulations were significantly shorter than those of the commercial tablet formulation ($p < 0.05$).

Accelerated stability studies: The effects of accelerated storage conditions on the mechanical properties and disintegration of the prepared ODT formulations were investigated. There were no significant differences between the fresh and aged formulations (data not shown). These findings indicate that the prepared ODT exhibit good mechanical and physical properties.

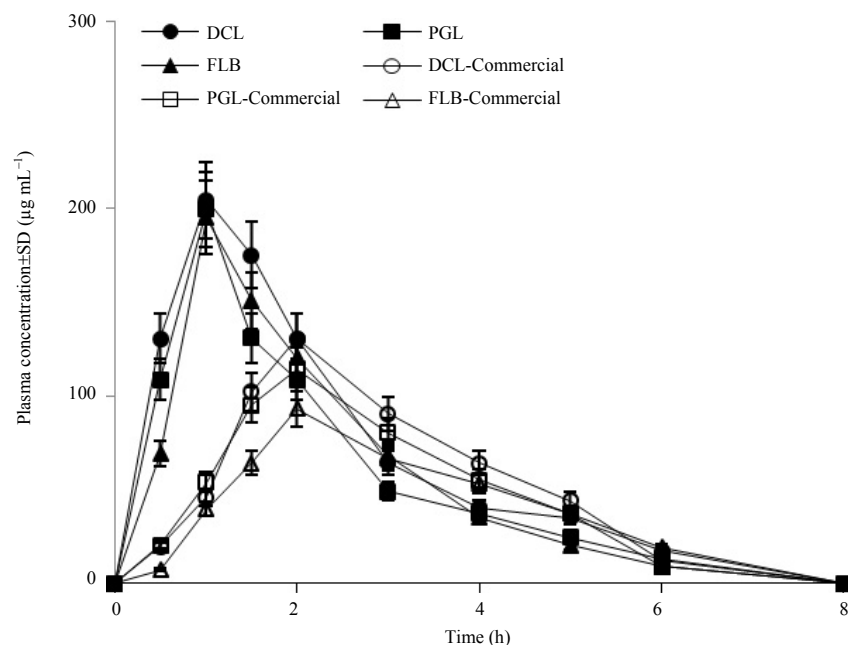


Fig. 3: Mean plasma concentration-time profiles of DCL, PGL and FLB after administration of ODT formulations or their respective commercial tablet to albino rabbits. The values were calculated in triplicate

DISCUSSION

The measured solubility values of FLB, DCL and PGL were in a good agreement with their pKa values. The drug solubility of the investigated drugs were minimum at pH 1.2 and increased with increasing pH of the medium due to increased drug ionization (Table 2). Lack of changes in the thermograms of the physical mixtures of the investigated drugs compared to their corresponding unprocessed powders indicates no evidence of interactions between the drugs and the employed excipients. Therefore, the excipients are not expected to impinge therapeutic action of the drugs.

The measured compressibility indexes and angles of repose indicate that the drug powders have moderate to poor flowability⁸. The results shown in Table 3 are in a good agreement with those for particle sizes measurements. The values of the true, bulk and tapped densities showed that the drug powders possessed maximum packing density that might be achieved under the influence of external applied forces. Hence, the overall factors might suggest that the powders could be better compacted into a durable tablet form with correct mathematical strength, porosity and disintegration for an orally fast dissolved tablet formulation. Wet granulation technique adopted in this study would be a viable option

to enhance flowability and compressibility by increasing particle sizes through granulation. According to the European and US pharmacopeias, the crushing strength values shown in Table 4 are well acceptable for ODT formulations. These values are sufficient to achieve enough strength for the tablets to face shocks during handling while maintaining fast disintegration upon administration³.

Wetting process of the ODT formulations is closely related to the internal structure and compaction of the tablets in addition to the amount and nature of the used excipients. Maltodextrin, being highly hydrophilic, is the main issue of the rapid wetting of the formulations and fast drug release from the tablet core. Amongst the investigated drugs, DCL showed the highest water absorption ratio and the shortest wetting time that might be ascribed to the more hydrophilic nature of diclofenac sodium. Disintegration time is considered one of the most important concerns for ODT formulations. Due to water absorbing nature of the superdisintegrants, maltodextrin and crosscarmilose sodium, the tested formulations exhibited rapid disintegration both *in-vitro* and in the oral cavity. The recorded disintegration times ranged from 33-50 sec in the order DCL < PGL < FLB (Table 5). This finding is attributed to the swelling of

the excipients which facilitates pushing the drug out of the tablet core even in the absence of additional water for administration. Furthermore, a good correlation ($R^2 = 0.986$) was recorded for *in-vitro* and oral disintegration time.

The reported HPLC technique for FLB, DCL and PGL drugs might provide several advantages of simplicity, high specificity, accuracy and very short run-cycle time. It could also be suggested that the method might be used for the routine quality control analysis of DCL, PGL and FLBF pure drugs and their dosage forms. It might be suggested that the fast absorption and high plasma levels of the investigated drugs after oral administration of the prepared ODT formulations to albino rabbits is attributed to the rapid disintegration and drug release in the rabbit saliva.

CONCLUSION

Maltodextrin is a promising excipient for preparation of orally disintegrating tablet formulations with good mechanical properties, rapid disintegration and drug release. The finding makes ODT more impending formulation for rapid delivering of FLB, DCL and PGL through the oral mucosa which might be the most buoyant approach to reduce hepatic metabolism of ingested drugs.

REFERENCES

1. Alderborn, G., 2007. Tablets and Compaction. In: Aulton's Pharmaceutics: The Design and Manufacture of Medicines, Aulton, M.E. (Ed.). 3rd Edn., Churchill-Livingstone, London, UK, ISBN-13: 978-0443101083, pp: 441-482.
2. FDA., 2008. Guidance for Industry: Orally disintegrating tablets. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), USA., December 2008.
3. Elnaggar, Y., M.A. El-Massik, O.Y. Abdallah and A.R. Ebian, 2010. Maltodextrin: A novel excipient used in sugar-based orally disintegrating tablets and phase transition process. *AAPS PharmSciTech*, 11: 645-651.
4. Kuno, Y., M. Kojima, H. Nakagami, E. Yonemochi and K. Terada, 2008. Effect of the type of lubricant on the characteristics of orally disintegrating tablets manufactured using the phase transition of sugar alcohol. *Eur. J. Pharmaceut. Biopharmaceut.*, 69: 986-992.
5. Mizumoto, T., Y. Masuda, T. Yamamoto, E. Yonemochi and K. Terada, 2005. Formulation design of a novel fast-disintegrating tablet. *Int. J. Pharmaceut.*, 306: 83-90.
6. Sunada, H. and Y. Bi, 2002. Preparation, evaluation and optimization of rapidly disintegrating tablets. *Powder Technol.*, 122: 188-198.
7. Llinas, A., J.C. Burley, K.J. Box, R.C. Glen and J.M. Goodman, 2007. Diclofenac solubility: Independent determination of the intrinsic solubility of three crystal forms. *J. Med. Chem.*, 50: 979-983.
8. Abdelkader, H., O. Y. Abdalla and H. Salem, 2008. Formulation of controlled-release baclofen matrix tablets II: Influence of some hydrophobic excipients on the release rate and *in vitro* evaluation. *AAPS PharmSciTech*, 9: 675-683.
9. Akhlaq, M., G.M. Khan, A. Wahab, A. Khan, A. Hussain, A. Nawaz and H.A. Abdelkader, 2011. A simple high-performance liquid chromatographic practical approach for determination of flurbiprofen. *J. Adv. Pharm. Technol. Res.*, 2: 151-155.