THE EFFECT OF DIFFERENT EXCIPIENTS ON LORNOXICAM/BACLOFEN ORODISPERSABLE TABLET

[1]Maryam Alaayedi*, [2]Ashti M.H. Saeed, and [1]Hasanain Mahmood*,
[1] Kerbala University, college of pharmacy, Kerbala, Iraq
[2] University of Mustansiriyah/ College of Pharmacy, Baghdad, Iraq

ABSTRACT

Background and aim: An orally disintegrating tablet (ODT) is different than ordinary tablets since it was designed to be disintegrated in the mouth cavity rather than swallowed to stomach. ODT has been used for elder, children and patients who have swallowing difficulty. Lornoxicam is a non-steroidal anti-inflammatory drug which used as analgesic, anti-pyretic and anti-inflammatory agent. Baclofen is used as a muscle relaxant; therefore, adding baclofen to lornoxicam in the same dosage form unit could both help improve certain musculoskeletal problems and improve patient compliance. The aim of this study was to formulate ODT of lornoxicam/baclofen containing different amount and types of disintegrating agent.

Method: Ten formulas of lornoxicam/baclofen ODTs using different excipients and superdisintegrants including crospovidone (CP), sodium starch glycolate (SSG), croscarmellose (CC) and banana powder in different concentrations. Different evaluation tests were performed for the tablet formulations involving tablet hardness, friability, content uniformity, weight variation, thickness, tablet disintegration and dissolution test.

Results and conclusion: The results demonstrated that formula containing 5% of SSG has a better formula with disintegration time of 15 seconds and better percent of drug release reaching more than 99% of lornoxicam and more than 95% of baclofen after 45 minutes of dissolution study. All formulas have acceptable results except tablets containing banana powder since their disintegration times were more than 5 minutes.

Keywords: ODT, lornoxicam, baclofen, disintegrating agents and banana powder.

تاثير المواد المختلفة على قرص تفكك فموي للورنوكسيكام/ باكلوفين

مريم العايدي جامعة كربلاء/ كلية الصيدلة، اشتي سعيد الجامعة المستنصرية/ كلية الصيدلة ، حسنين محمود جامعة كربلاء/ كلية الصيدلة

الخلاصة

الخلفية والهدف: قرص تفكك فموي الذي يختلف عن أقراص عادية منذ تم تصميمه ليتم تفكك في تجويف الفم بدلا من ابتلاع في المعدة. وقد استخدمت هذه الاشكال للمسنين والأطفال والمرضى الذين لديهم صعوبة في البلع. لورنوكسيكام هومن الادويه الغير الستيرويدية المضادة للالتهابات التي تستخدم مسكن، ومكافحة الحمى والمضادة للالتهابات. يستخدم باكلوفين لاسترخاء العضلات. وبالتالي، إضافة باكلوفين إلى لورنوكسيكام في الشكل الدوائي نفسه يمكن أن تساعد على

حد سواء تحسين بعض المشاكل العضلية الهيكلية وتحسين الامتثال المريض. وكان الهدف من هذه الدراسة صياغة حبوب فمويه ذائبه من لورنوكسيكام / باكلوفين تحتوي على كمية وأنواع مختلفه من عوامل التفكك.

الطريقه: عشرة فورملات من لورنوكسيكام / باكلوفين حبوب فمويه ذائبه تحضر باستخدام اضافات مختلفة و عوامل تفكيك بما في ذلك كروسبوفيدون، الصوديوم النشا غليكولات،كروسكارملوز ومسحوق الموز بتركيزات مختلفة. تم إجراء عدد من اختبارات التقييم للحبوب الفمويه التي تتضمن قياس صلابة الحبوب ، القابلية للتفتيت، توحيد المحتوى، تباين الوزن، سمك، تفكك الشكل المحضر واختبار الانحلال.

النتائج والاستنساخ : وأظهرت النتائج أن الحبوب المحضره ذوات النسبه 5٪ من نشا صوديوم كلايكوليت يكون أفضل تفكك حيث كان الوقت اللازم للتفكيك 15 ثانية ونسبة أفضل لتحرر الدواء وتصل إلى أكثر من 99٪ من لورنوكسيكام وأكثر من 95٪ من باكلوفين بعد 45 دقيقة من بدء التحرر . جميع الصيغ، لها نتائج مقبولة باستثناء أقراص تحتوي على مسحوق الموز لانها تحتاج وقت التفكك يصل لأكثر من 5 دقائق.

مفاتيح الكلمات: قرص تفكك فموي ، لورنوكسيكام، باكلوفين، مواد مفتتة للحبة.

1. INTRODUCTION

Oral disintegrating tablet (ODT) is a solid dosage form which disintegrates rapidly in the oral cavity after absorbing small amounts of saliva (1). Hence, it can be preferred by people having swallowing difficulty including children and elder. ODT relays on the presence of disintegrating agents (superdisintegrants) in the formulation. An appropriate disintegrating agent is a key aspect in the ODT dosage form development. There are many types of superdisintegrants available including natural and synthetic substances such as gellan gum (natural) and sodium starch glycolate (synthetic) (2-4). Drug bioavailability depends on drug absorption. In case of poorly water-soluble drugs, the bioavailability of the drug depends mainly on its dissolution that affected by drug dosage form disintegration. Therefore, ODT formulation could help enhance the dissolution, then improving the bioavailability of these drugs (5). Lornoxicam is a non-steroidal anti-inflammatory drug which has analgesic, antipyretic and anti-inflammatory characteristics. It is used for different pain types including pain resulted from the joints inflammatory disorders, osteoarthritis and others. Lornoxicam is class II in biopharmaceutical classification system which has low water solubility, therefore; formulation of drug such as ODT could improve its solubility then bioavailability. In addition, it can bypass the liver metabolism, when absorbed via oral mucosa (6, 7).

Furthermore, many joints diseases associated with muscle spasm, therefore; adding anti-muscle contraction (skeletal muscle relaxant) like baclofen could help relief patients' musculoskeletal pain. Baclofen is used to help relieve the spasms, cramping, and tightness of muscles since it relaxing skeletal muscles in the body (8). Adding baclofen to lornoxicam in the same dosage form unit could both help improve certain joint diseases (musculoskeletal pain) and improve patient compliance.

The aim of this study was to formulate ODT of lornoxicam/baclofen containing different amount and types of disintegrating agent.

2. MATERIALS AND METHODS

2.1. Materials

Lornoxicam, baclofen and magnesium stearate (MS) were purchased from Baoji Guuokang Bio-Technology Co., Ltd (China). Crospovidone, sodium starch glycolate, croscarmellose and banana powder were bought from Wuhan Senwayer Century Chemical Co., Ltd (China). Mannitol was from Thomas Baker Chemicals PVT. Ltd (India). Sucralose was from Shanghai Ruizheng Chemical Technology Co., Ltd. (China).

2.2. Methods

2.2.1. Formulation of ODT

Lornoxicam/baclofen ODT had been made by direct compression method using a single punch tablet machine (spindle-shaped resulted tablet). Lornoxicam, baclofen, disintegrating agents, mannitol, sucralose, and MS were blended uniformly together by geometric trituration, then compressed directly by tablet machine (7). The ten ODT formulas of lornoxicam/baclofen were prepared according to Table 1.

Table 1: Lornoxicam/baclofen ODT formulations.

Ingredient (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Lornoxicam	8	8	8	8	8	8	8	8	8	8
Baclofen	10	10	10	10	10	10	10	10	10	10
Crospovidone	15	30	45	-	-	-	-	-	-	-
Sodium starch glycolate	-	-	-	12	15	-	-	-	-	-
Croscarmellose	-	-	-	-	-	15	20	30	-	-
Banana powder	-	-	-	-	-	-	-	-	12	15
Mannitol	261	246	231	264	261	261	236	246	264	261
Sucralose	3	3	3	3	3	3	3	3	3	3
MS	3	3	3	3	3	3	3	3	3	3
Total Weight	300	300	300	300	300	300	300	300	300	300

2.2.2. Evaluation the flowability of the pre-compressed tablet blend powder

Two tests were performed to determine flow characteristics of the powder blend of the tablet formulas which were the angle of repose and compressibility index (Carr's index). The first one was performed using petri dish and funnel, where the powder blend of each formula allowed to freely flowing over a known diameter petri dish through the fixed funnel. The angle of repose was calculated using the following equation:

$$\text{Tan } Ø = h/r$$

Where Ø is the angle, *h* is the height of the resulted con after pouring and *r* is the radius of the Petri dish (9).

Compressibility index was done by pouring the powder blend of each formula into a 10 ml capacity cylinder to measure the initial bulk volume (V_0), then the cylinder tapped until the volume of the powder become constant (V_t). The index was calculated according to the equation below (9):

$$\text{Compressibility Index} = [(V_0 - V_t)/ V_0] * 100$$

2.2.3. Evaluation of ODT tablet

2.2.3.1. Friability of tablet

Friability test was applied to each formula using MIN HUA CS-2 friability test apparatus (China). Twenty tablets of each formula were weighted and placed in the apparatus and rotated 25 rpm for 4 minutes, then the tablets weighted again and the percent of friability calculated using the equation below:

$$\% \text{ Friability} = (W_0 – W)/ W_0 \times 100$$

Where W_0 is the weight of the tablet before the test, W is the weight of the tablets after the test (10).

2.2.3.2. Hardness of tablet

Digital hardness tester (MINHUA Pharmaceutical Machinery Co., Ltd., China) was used to measure the hardness of the ODT of lornoxicam/baclofen. The hardness of three tablets of each formula was measured and the mean calculated.

2.2.3.3. Thickness of tablet

Manual micrometer (Guo Gen, China) was used to measure the ODT core centre thickness. Three tablets of each formula were evaluated, then mean obtained.

2.2.3.4. Weight variation

Twenty tablets of each formula were chosen randomly and weighted individually. The average weight of these 20 tablets were calculated, then individual tablet weight compared with the average (10).

2.2.3.5. Wetting time

This test was performed using folded filter paper and the tablet was placed inside it. Then, they were put in a petri dish filled with 5 ml of aqueous amaranth solution. The wetting time represented the time required for the tablet to wet by this solution (9, 11-13).

2.2.3.6. Drug Content

Ten tablets of each formula were grand individually and amount of powder equivalent to the drugs content (lornoxicam 8 mg and baclofen 10 mg) were taken separately and

solubilized in phosphate buffer (pH 6.8) and analysed using UV spectrometer to quantify the amount of the drugs, using the regression equation of the calibration curves of each drugs at their lambda max (10).

2.2.3.7. Disintegration time of ODT

The disintegration time of the ODT was performed using disintegration apparatus (MINHUA Pharmaceutical Machinery Co., Ltd., China). A tablet was put in a special tubed place which moved up/down in 900 ml buffer of pH 6.8 at 37^{o}C (13, 14).

2.2.3.8. In vitro drug release study

Lornoxicam and baclofen release from the ODT was performed using USP type II (paddle type) dissolution test apparatus (MINHUA Pharmaceutical Machinery Co., Ltd., China). The ODT was placed into the dissolution apparatus bowl which full of 900 ml of the buffer (pH 6.8) at 37^{o}C and the paddle rotation was 50 rpm. Samples of 5 ml were taken at a specific time interval during 45 minutes and replaced with the same amount of fresh phosphate buffer, the samples were analysed spectroscopically at the lornoxicam and baclofen lambda max using the UV spectrophotometer regression equation of the drugs calibration carves at their lambda max (9, 11).

2.2.4. Drug-excipients interaction

Determination of the compatibility between the pure lornoxicam, baclofen and other used excipients in the formulation was performed using the Fourier-transform infrared spectroscopy (FTIR). The powder of the drugs and the excipients were homogenized with IR grade potassium bromide, the pellets which resulted, were scanned over the wavelength range of 4000-400 cm^{-1}.

2.2.5. Statistical analysis

One-way ANOVA (GraphPad Prism software version7.00, USA) was followed in this work for statistical analysis of the results. The difference is considered statistically significant when $P < 0.05$.

3. RESULTS AND DISCUSSION

3.1. Angle of repose and Carr's index

The results of these two tests represent in Table 2. It is demonstrated that the powder blend of all formulations has accepted (good to excellent) flow properties to be compressed directly by tablet machine with the angle of repose range of (25-30.6) and Carr's index range of (8.7-12.8) (9, 11).

Table 2. Rheology characteristics of the ODT formulas powder blend, all results represent mean ± SD (n=3).

Formula No.	Angle of repose	Carr's index
F1	25 ± 2	11 ± 1
F2	27 ± 1	10.3 ± 0.3
F3	26.3 ± 3	11.6 ± 0.3
F4	27.4 ± 2	12 ± 0.7
F5	26 ± 1	9.1 ± 1
F6	29 ± 2	8.7 ± 0.9
F7	27.2 ± 0.5	8.9 ± 0.5
F8	29.1 ± 1	10.4 ± 0.6
F9	28 ± 0.4	12 ± 0.3
F10	30.6 ± 1.8	12.8 ± 0.2

3.2. Evaluations of the ODT

3.2.1. General ODT characteristics

Ten formulations were developed to get optimized ODT of the lornoxicam/baclofen combination. All tablets were evaluated and the main tests results represent in Table 3. Mannitol was used as diluent due to its nature (sugar) and required characteristics including stability, crucial qualities, and inert. Different disintegrating agents were used. Ordinary tablet evaluation tests were made. The hardness test of ODT was within the ordinary tablet hardness range (4 ± 0.05 to 5.8 ± 0.16) kg/cm^2. The friability test results were within the accepted range (<1%) proving that the tablets would be stable for shipping and handling (no dusting). Moreover, the weight variation and drugs content were within required accepted range (±5%) (10).

Disintegration time is one of the main evaluation tests of the ODT since it should disintegrate within the seconds in the mouth cavity. Most formulations presented results of time less than 30 seconds except two formulas which involved banana powder as a disintegrating agent. It prolongs the tablet disintegration and increasing its amount in the tablet, increased the time for disintegration due to its low ability to wick in saliva; therefore, it could not be used as superdisintegrant (banana powder acted as binder at 10% or more since it rich with starch) and this is different than the presently available research studies (15-18). However, using CP, SSG, and CC in different concentrations were improve disintegration. ODT containing 5% of SSG (F5) showed the shortest time of disintegration (15 seconds). This is because of its ability to absorb saliva and improve tablet disintegration (19-21). Formulations containing SSG had shorter wetting time which reflects the disintegration pattern and time for the ODT.

CC and SSG are cross-linking polymers which rapidly swell when they get in contact with water without gel formation. This swelling leading to a high change in hydrostatic pressure

in the tablet, then disintegration period. CP absorbs water rapidly without swelling leading to tablet disintegration (2, 22). On the other hand, Increase the CP and CC concentrations did not significantly change (increase or decrease) the disintegration time of the tablets. However, increase SSG from 4% to 5% significantly could decrease the disintegration time from 25 sec to 15 sec.

Table 3. The general parameters of different formulations of lornoxicam/baclofen ODT, all results represent as mean ± SD (*n* = 3).

Formulas	Thickness (mm ± SD)*	Weight variation (g ± SD)***	Friability (% ± SD)*	Hardness (kg/cm^2 ±SD)*	Drug content (% ±SD)**		Wetting time (seconds ±SD)*	DT (second±SD)*
					Lornoxicam	Baclofen		
F1	25.2 ± 0.2	0.301 ± 0.005	0.5 ± 0.01	4 ± 0.05	98.6 ± 0.4	96.4 ± 1.05	31 ± 1	26 ± 2
F2	25.1 ± 0.2	0.300 ± 0.034	0.3 ± 0.003	4.2 ± 0.04	99.7 ± 1.3	95.1 ± 0.98	35 ± 2	29 ± 3
F3	25 ± 0.4	0.302 ± 0.005	0.31 ± 0.02	4.79 ± 0.05	98.3 ± 0.5	95.3 ± 2.15	26 ± 3	24 ± 4
F4	24.9 ± 0.2	0.297 ± 0.002	0.6 ± 0.005	4 ± 0.1	99.8± 0.4	98± 0.8	34 ± 2	25 ± 1
F5	25.4 ± 0.3	0.309 ± 0.021	0.14 ± 0.007	4.1 ± 0.05	96 ± 1.3	95 ± 0.22	19 ± 1	15 ± 1
F6	25.3 ± 0.1	0.309 ± 0.024	0.32 ± 0.006	4.52 ± 0.07	95.5 ± 0.7	94.5 ± 0.94	34 ± 2	22 ± 2
F7	25.1 ± 0.3	0.301 ± 0.012	0.65 ± 0.002	4.5 ± 0.17	95.7 ± 1.01	95.1 ± 0.98	39 ± 1	30 ± 2
F8	25.4 ± 0.1	0.298 ± 0.007	0.44 ± 0.004	4.9 ± 0.14	96.8 ± 0.5	98.1 ± 1.5	37 ± 3	21 ± 1
F9	25.2 ± 0.3	0.299 ± 0.002	0.3 ± 0.005	5.3 ± 0.17	95.3 ± 0.46	95.1 ± 1.34	421 ± 4	410 ± 5
F10	25.2 ± 0.1	0.301 ± 0.018	0.55 ± 0.003	5.8 ± 0.16	96.2 ± 1.9	95.6 ± 1.28	551 ± 6	543 ± 4

***n=3, **n=10, ***n=20**

3.2.2. In-vitro drug release studies

The drug release from the tablets was evaluated using dissolution apparatus for 45 minutes. Lornoxicam and baclofen release from the formulated tablet shown in Figure 1 and 2, respectively. The results showed that all formulations release more than 85% of lornoxicam and more than 60% of baclofen at the end of the study. Formulations F1-F8 released most of the drugs in the first 10 minutes of the study, while F9 and F10 release the drug slowly since they contain a banana powder which slows the tablet disintegration then dissolution.

The disintegration affects the dissolution, rapid dissolution of F1-F8 since they had short disintegrating time. F9 and F10 had slow dissolution especially in the first 10 minutes since they had long disintegration (5).

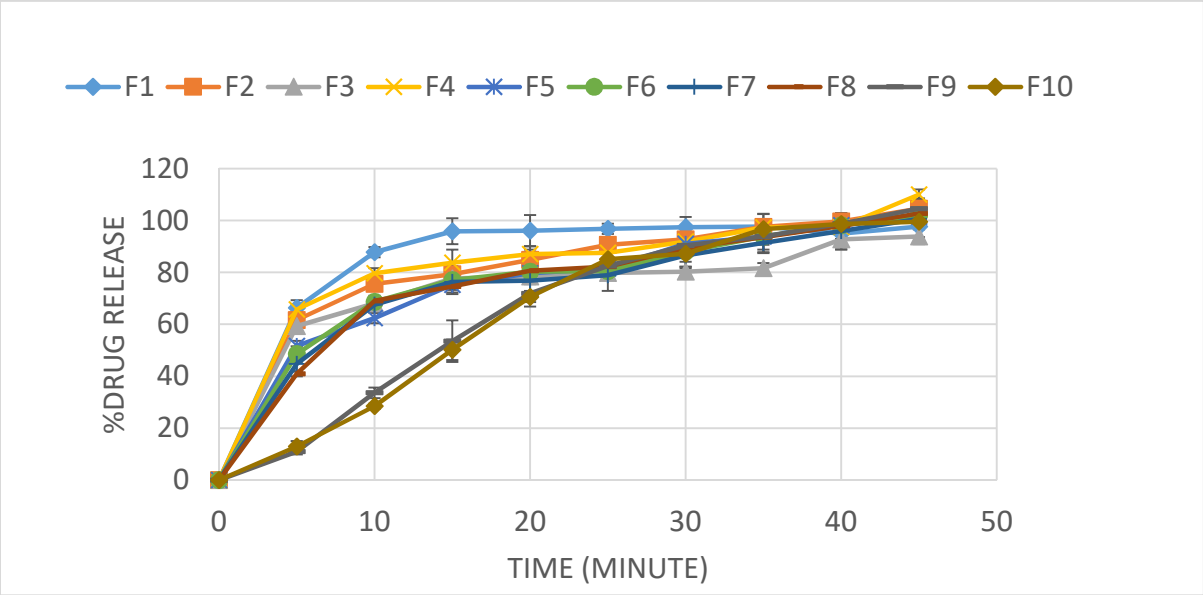

Figure 1. Percent of lornoxicam release of different ODT formulas in 900 ml phosphate buffer (pH 6.8) at 37°C, the results represent mean percent of drug released± SD (n=3).

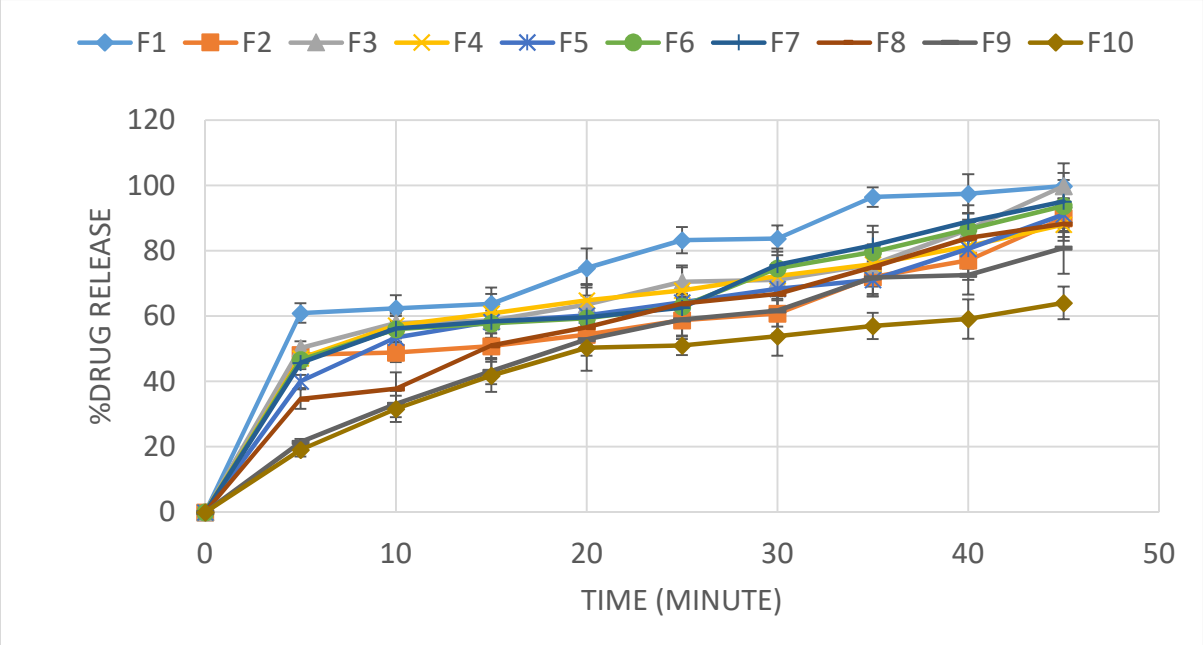

Figure 2. Percent of baclofen release of different ODT formulas in 900 ml phosphate buffer (pH 6.8) at 37°C, the results represent mean percent of drug released± SD (n=3).

3.3. The drugs-excipients compatibility study

There was no interaction between the two drugs and between the drugs and the used excipients because the identifying peaks of the drugs were available (23, 24), as shown in Figure 3.

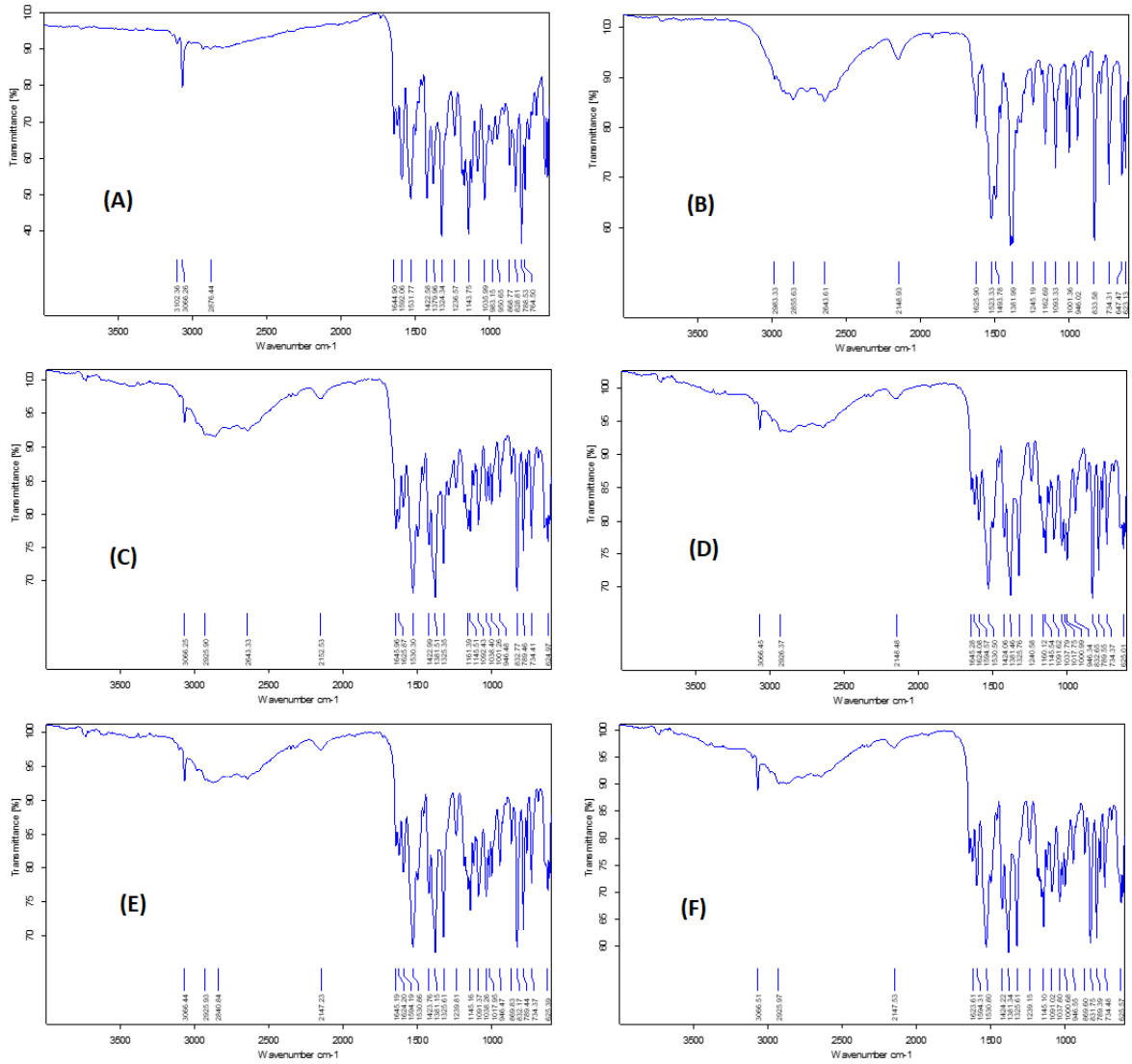

Figure 3. Drugs and other excipients FTIR spectra, where (A) represents lornoxicam, (B) Baclofen, (C) lornoxicam, baclofen and croscarmellose mixture, (D) lornoxicam, baclofen, and SSG, (E) lornoxicam, baclofen and crospovidone and (F) lornoxicam, baclofen, and banana powder mixture.

4. CONCLUSION

ODTs of lornoxicam and baclofen combination were formulated with different types and concentration disintegrating agents. Formulas of the three synthetic superdisintegrants (CP, SSG, and CC) had a disintegration time of less than 30 sec since they rapidly bursted when they got in contact with water which then facilitatess disintegration. Tablet with 5% SSG had the shortest disintegration time of 15 sec. However, the only natural disintegrate, banana powder, had a long disintegration time of 7 and 9 min for 4% and 5%, respectively that may be due to its binding effect.

5. REFERENCES

1. Nishiyama T, Ogata T, Ozeki T. Preparation of bitter taste-masking granules of lafutidine for orally disintegrating tablets using water-insoluble/soluble polymer combinations. Journal of Drug Delivery Science and Technology. 2016;32:38-42.

2. Priyanka S, Vandana S. A review article on: superdisintegrants. International Journal of Drug Research and Technology. 2017;3(4):11.

3. Sharma V, Arora V, Ray C. Use of Natural superdisintegrant in Mouth Dissolving Tablet An Emerging Trend. International bulletin of drug research. 2010;1(2):46-54.

4. Rawat S, Derle D, Fukte SR, Shinde PR, Parve BS. Superdisintegrants: An overview. World J Pharm Pharm Sci. 2014;3(5):263-78.

5. Sravani S, Sailaja P. Formulation and Evaluation of Fast Dissolving Tablets of Felodipine. IOSR Journal Of Pharmacy. 2016;6(7):104-12.

6. Anumolu PD, Sunitha G, Hima Bindu S, Satheshbabu PR, Subrahmanyam CVS. Development and Validation of Discriminating and Biorelevant Dissolution Test for Lornoxicam Tablets. Indian J Pharm Sci. 2015;77(3):312–20.

7. Patel DM, Shah HR, Patel RJ, Patel CN. Preparation and characterization of lornoxicam co-crystals. World J of Pharm and Pharm Sci. 2014;3(6):713-32.

8. Radke R, Jadhav J, Chajeed M. Formulation and evaluation of orodispersible tablets of baclofen. Int J Chem Tech Res. 2009;1(3):517-21.

9. Elkhodairy KA, Hassan MA, Afifi SA. Formulation and optimization of orodispersible tablets of flutamide. Saudi Pharmaceutical Journal. 2014;22(1):53-61.

10. XXIII UP, editor The United States Pharmacopeia. Twentieth Revision, United States Pharmacopeia Convention, Rockville, MD; 1995.

11. Amelian A, Szekalska M, Wilczewska AZ, Basa A, Winnicka K. PREPARATION AND CHARACTERIZATION OF ORALLY DISINTEGRATING LORATADINE TABLETS MANUFACTURED WITH CO-PROCESSED MIXTURES. Acta poloniae pharmaceutica. 2016;73(2):453-60.

12. Ranganathan V, Yoong J. Development and Evaluation of Mouth Dissolving Tablets using NaturalSuper Disintegrants. Journal of Young Pharmacists. 2017;9(3):332.

13. Malik K, Arora G, Singh I. Locust bean gum as superdisintegrant–formulation and evaluation of nimesulide orodispersible tablets. Polimery w medycynie. 2011;41(1):17-28.

14. Okuda Y, Irisawa Y, Okimoto K, Osawa T, Yamashita S. Further improvement of orally disintegrating tablets using micronized ethylcellulose. International journal of pharmaceutics. 2012;423(2):351-9.

15. Alam MT, Parvez N, Sharma PK. FDA-Approved natural polymers for fast Dissolving Tablets. Journal of pharmaceutics. 2014;2014.

16. Soni A, Raju L. Formulation and evaluation of fast disintegrating tablet containing hydrochlorothizide. Indian Journal of Pharmacy and Pharmacology. 2015;2(2):119-33.

17. Waliszewski KN, Aparicio MA, Bello LsA, Monroy JA. Changes of banana starch by chemical and physical modification. Carbohydrate polymers. 2003;52(3):237-42.

18. Ssonko UL, Muranga FI. Partial characterization of starches from major banana (matooke) cultivars grown in Uganda. Food science & nutrition. 2017;5(6):1145-53.

19. Shihora H, Panda S. Superdisintegrants, utility in dosage forms: a quick review. J Pharm Sci Biosci Res. 2011;1(3):148-53.

20. Mangal M, Thakral S, Goswami M, Ghai P. Superdisintegrants: An updated review. International journal of pharmacy and pharmaceutical science research. 2012;2(2):26-35.

21. Jagdale S, Fernandes N, Kushekar B, Shah T, Chabukswar A. Selection of superdisintegrant for Famotidine rapidly disintegrating tablets. J Chem Pharm Res. 2010;2(2):65-72.

22. Kumar G, Nirmala R. Fundamental aspects of superdisintegrants: a concise review. Journal of Global Pharma Technology. 2012;4(02):1-12.

23. Kolhe S, Ranade A. Development and Evaluation of Bilayer Gastroretentive Floating Drug Delivery System for Baclofen. Ind J Pharm Edu Res. 2013;47(1):41.

24. Acharya A, Ahmed MG, Rao BD, CH V. Development and Evaluation of Ethosomal Gel of Lornoxicam for Transdermal Delivery: In-Vitro and In-Vivo Evaluation.