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SALT AND NON-SALT FORMING EXCIPIENTS TO IMPROVE THE DISSOLUTION OF DEXIBUPROFEN; FORMULATION OF CHEWABLE TABLETS

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ABSTRACT
Dexibuprofen is a stronger non-steroidal anti-inflammatory drug than ibuprofen but with less gastric damage. However, it suffers poor aqueous solubility. This work improved Dexibuprofen dissolution via co-processing with inert excipients with the aim of formulating chewable tablets. Wet co-grinding of Dexibuprofen with increasing proportions of mannitol or meglumine was performed after liberation from their ethanolic solutions. The prepared mixtures were investigated using differential scanning calorimetry, Fourier Transform Infrared spectroscopy, powder X-ray diffraction and dissolution behavior. Optimum co-processed mixtures were prepared into chewable tablets after addition of suitable additives. Wet co-grinding improved drug dissolution parameters compared to unprocessed one, with meglumine being superior to mannitol. Solid state characterizations reflected possible salt formation between the drug and meglumine. For mannitol mixtures, dissolution enhancement was attributed to partial amorphousization of Dexibuprofen along with particle size reduction. The selected co-processed mixtures were successively formulated into chewable tablets. *In vitro* dissolution studies were performed using crushed as well as intact tablets. Mannitol based tablets showed prompt drug release in both cases. However, meglumine based tablets required crushing for fast drug release indicating the need for chewing. The study introduced simple co-processing as a tool to enhance dissolution rate of Dexibuprofen with subsequent formulation of chewable tablets.

KEYWORDS: Dexibuprofen, mannitol, meglumine, salt form, co-grinding.

INTRODUCTION
Oral ingestion is the most convenient and commonly used route of drug delivery due to its ease of administration, high patient compliance, cost effectiveness, least sterility necessity, and flexibility in the dosage form design.[1] One of the important drawbacks of this dosage form is Dysphagia or difficulty in swallowing for many patients especially in pediatric, geriatric and mentally ill patients.[2] Additionally, the poor aqueous solubility of the active pharmaceutical ingredient (API) forms the major hurdle for successful development process of an oral dosage form. In such cases, low dissolution rate, with subsequent partial and non- uniform absorption limits the drug exposure at its active site and constrains its clinical effectiveness.[3]

The development of chewable tablets allows more rapid release and more rapid absorption of active ingredients so provide quick onset of action.[4] They are broken down in the mouth and release their ingredients in the process, so do not have much lag time as required for the disintegration of tablets before absorption from stomach.[5] This dosage form can provide additional advantage and convenience for children, elderly patients with swallowing difficulties and can be administered in the absence of potable liquids.[6]

Dexibuprofen is a non-steroidal anti-inflammatory drug.[7] It is the active dextrorotatory enantiomer of ibuprofen with reported better anti-inflammatory effects than ibuprofen with less gastric damage.[8] It is mainly used to manage mild-to-moderate pain and inflammatory conditions, such as headache, postoperative pain, dysmenorrhea, dental pain, and soft tissue rheumatism.[9, 10] Dexibuprofen belongs to class II of the Biopharmaceutical Classification System (BCS) having low water solubility which is the rate limiting step in absorption of drug.[11, 12] It has a Log P of 3.97 (n-octanol/water) and pka value of 4.65.[13] Its absorption occurs throughout the GI tract after oral administration. So, the low solubility of Dexibuprofen in the gastric pH decreases its bioavailability as the drug cannot be absorbed unless it is in a solution form.[11]

Accordingly, the objective of this work was to enhance the dissolution rate of Dexibuprofen. This will be achieved via wet co-grinding the drug with pharmaceutically acceptable excipients with the aim of

modifying the drug crystals or basic nature. This technique was previously adopted to enhance drug dissolution;[14, 15] The selected excipients were mannitol and meglumine. The former is sugar alcohol and was selected as a potential co-crystal conformer. Meglumine (A derivative of sorbitol in which the one of its hydroxyl group is replaced by a methylamino group) was investigated as a potential co-crystal conformer as well as salt forming agent. These excipients were selected based on their hydrophilic nature and their ability to modify drug crystalline structure or its basic nature which can improve the dissolution of the selected drug;[16, 17] The use of alkaline excipient can be taken as a mean for enhanced dissolution rate of acidic drug;[18] Chewable tablets with subsequent fast drug release were prepared using optimized co-grinded mixtures.

MATERIALS AND METHODS

Materials

Dexibuprofen raw material was a gift sample from Future Pharmaceutical Industries (FPI) (Badr city, Cairo, Egypt). Mannitol (powder), and crospovidone were kindly obtained from Sigma Pharmaceutical Co. (Quesna, Egypt). Meglumine, granular mannitol and avicel PH102 were obtained as gift samples from Amoun for Pharmaceutical Industries (Alobour city, Cairo, Egypt). Aerosil 200 was supplied as a gift sample from Pharco Pharmaceutical Industries (Egypt).The buffer salt, magnesium stearate, potassium hydroxide and ethanol were purchased from El Nasr Pharmaceutical Chemicals Co. (Cairo, Egypt).

Methods

Construction of standard curve

A stock solution of Dexibuprofen (1mg/ml) in ethanol was prepared. Serial dilutions were prepared to obtain concentrations of 7.5, 10, 15, 20, 25 µg/ml. The prepared samples were analyzed spectrophotometrically at λ max of 222 nm using UV spectrophotometer (ThermoFisher Scientific, Evo300pc, USA). The constructed standard curve showed linear relationship (R^2=0.999) between the concentration and the absorbance (Y= 0.0441x + 0.0134).

Formulation of Dexibuprofen co-ground mixtures

The composition of the prepared formulations is presented in Table 1. Ethanol-assisted co-grinding technique was adopted for the formulation of different drug crystals by grinding the drug with the selected additives (at different molar ratios) using mortar and pestle.[19] Ethanol was added drop wise till the formation soft paste. Grinding was continued until dry powder was obtained. The products were kept in a desiccator overnight, to ensure complete evaporation of the organic solvent, followed by storage in tightly closed containers until required. The pure drug similarly manipulated and was taken as positive control to estimate to effect of the added excipient.

Table 1: Compositions of the prepared formulations presented as both molar and weight ratios, together with the dissolution parameters presented as amount released after 5 minutes (Q5) and dissolution efficiency (DE%).

Formulation	Drug	Mannitol	Meglumine	Q_5 (%)	DE_{60} (%)
Pure drug (negative control)	1	_	_	24.1 ± 1.7	66.2 ± 2.2
F1 (positive control)	1	_	_	43.3 ± 1.5	83.1 ± 0.4
F2	1(1)	1(0.8)	_	39.4 ± 1.0	68.5 ± 1.3
F3	1(1)	2(1.7)	_	49.8 ± 0.6	83.7 ± 1.7
F4	1(1)	3(2.6)	_	73.9 ± 3.1	90.7 ± 0.0
F5	1(1)	4(3.5)	_	80.7 ± 0.8	92.5 ± 0.3
F6	1(1)	_	1(0.9)	100 ± 0.3	95.8 ± 0.4

-Values between brackets represent the weight ratios in grams; positive control is wet grinded drug.

Characterization of the prepared formulations

Fourier–transform infrared spectroscopy (FTIR)

FTIR spectrophotometer (Bruker Tensor 27, Ettlingen, Germany) was employed to collect the IR spectra of raw Dexibuprofen, mannitol, meglumine and their formulations. Samples were mixed with a spectroscopic grade of potassium bromide prior to compressed into disk and subjecting to scanning in the range of 4000 to 400 cm^{-1}.

X-ray powder diffraction (XRPD)

XRPD pattern of raw Dexibuprofen, mannitol, meglumine and their formulations were recorded using a GNR APD 2000 pro-X-ray diffractometer. Samples were loaded into aluminum glass specimen holders. The X-ray data was collected using 2 theta scan axis at scanning step size of 0.03° and angular range of 3–60°.

Differential scanning calorimetry (DSC)

Thermal analysis of the raw Dexibuprofen, mannitol, meglumine and their co-grinded formulations was performed using a differential scanning calorimetry (Shimadzu DSC-50). The weighed amount of each sample was loaded into aluminum pans before being crimped. The thermal behavior of each sample was tested at a heating rate of 10ºC/min in the temperature range of 25-400ºC under nitrogen flow. The process was

conducted under computer control using TA-60WS thermal analysis workstation and software.

***In vitro* drug dissolution studies**

The dissolution rate of Dexibuprofen from different formulations (processed, unprocessed pure drug and wet grinded formulations), shown in Table 1, was monitored using the USP II dissolution apparatus (Copley, NG 42JY, Nottingham, UK). The rotation speed of the paddles was adjusted at 50 rpm and test was conducted for 1 hour. Amount equivalent to 200mg of the drug was loaded into the dissolution vessels containing 900 ml of dissolution medium (phosphate buffer (pH 7.2) kept at 37 ºC±0.5ºC). Aliquots of 5 ml of all samples were drawn at time intervals (5, 10, 15, 20, 30, 45 and 60 min) and compensated by fresh dissolution media to maintain constant volume. The withdrawn samples were instantly filtered using 0.45µm Whatman membrane. The filtrate was properly diluted, if necessary, with the fresh dissolution medium and assayed by UV spectrophotometer at 222 nm to determine the drug content. The % cumulative amount of Dexiboprofen dissolved was plotted as a function of time to obtain the dissolution profile. The dissolution parameters which were used for comparison included the percentage of the amount dissolved in the first 5 min (Q5) and the total dissolution efficiency (DE). DE was obtained from the area under the curve of the dissolution profile at time t using the nonlinear trapezoidal rule and expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time.[20] To compare between the dissolution profiles of different formulations, similarity factor test was employed using the following equation:

$$F_2=50\times\log\left\{\left[1+\frac{1}{n}\sum_{t-1}^{n}(Rt-Tt)^2\right]^{-5}\right\}\times 100$$

Where F_2 is the similarity factor value, n is the number of data points, Rt is amount of the reference (control) dissolved (%) at time t and Tt is the percentage amount of the test dissolved at the same time points.[21]

This test is used for dissolution profile comparisons and to justify if product performance is similar (f2 values >50) or dissimilar (f2 values <50) to the selected reference, under the same dissolution conditions.

Preparation of chewable tablets

The detailed compositions of the prepared tablets are shown in Table 2. The co-processed mixtures F3 and F6 were used to prepare the tablets. The former was selected as it was the optimum amount of mannitol based mixtures that can be used to prepare tablets. Higher mannitol ratio was very difficult to compress.

The calculated amount of selected formulations, equivalent to 200mg of Dexibuprofen was geometrically mixed with the excipients listed in Table 2 before direct compression into tablets using 14mm punch. This process employed a single punch tablet machine (Royal Artist, Kapadia Industrial Estate, BLDG, Mumbai, India). The compression force was adjusted to produce tablets having hardness 5-6 kp and each tablet was made to contain 200mg of the drug per tablet.

Table 2: Compositions of the prepared chewable tablets.

Ingredients (mg/tablet)	Mannitol Tab (mg)	Meglumine Tab (mg)
F3	553	_
F6	_	389
Mannitol (granular)	_	150
Avicel PH 102	173	187
Crospovidone	30	30
Magnesium stearate	12	12
Aerosil	25	25
Total tablet weight (mg)	793	793

Characterization of the powder blends

Prior to compression, tablet blends were subjected to flowability and compressibility studies to ensure suitability for tableting. The bulk density of each blend was measured by pouring a fixed weight (m) of powder blend into a graduated cylinder and noting the bulk volume (V_b). The bulk density was calculated by dividing mass over V_b ($P_b=M/V_b$). The tapped density was determined by tapping the same cylinder with the blend until the volume is no longer decreases (V_t). Tapped density P_t was similarly calculated. From these two densities, Carr's compressibility index (CI) as well as Hausner ratio (HR) were calculated using these equations: $CI=100(P_t-P_b)/P_t$, $HR=P_t/P_b$ respectively.[22]

Angle of repose was measured using the fixed funnel method. The powders were allowed to pour from a funnel whose tip being held at fixed distance from a glass tile. Powder pouring is stopped when the apex of the powder pile reaches the tip of the funnel. The height of the pile was then divided by half the width of the base. The inverse tangent of this ratio is the angle of repose (θ).

Evaluation of chewable tablets

Uniformity of weight: Twenty tablets were weighted individually and their average weight was calculated. The deviation of the each tablet from the calculated average was recorded. According to tablets weight, the acceptance criteria were taken as deviation from the

mean by ±5%. Tablet batch is considered agreeable with the USP test if no more than two tablets are outside the limit of ±5%, and no tablet differs by more than 10%.[23]

***Tablet friability*:** The friability of the tablets was measured in friabilator (Erweka, Heusenstamm, Germany). Pre-weighed tablets (10 tablets) were placed in the friabilator then exposed to 100 revolutions. The remaining intact tablets were carefully de-dusting and weighed again. The friability was calculated as the percentage weight loss. If the percent loss was below 1%, the tablets pass the test.[23]

Drug content: A content uniformity test was done to ensure drug uniformity of the compressed tablets. A randomly selected 10 tablets were individually subjected to the test. The tablets were considered acceptable if the content of each of at least 9 tablets was in the range of 85%-115% of the labeled amount of Dexibuprofen. The tenth tablet should not contain <75% or >125% of the labeled amount.[23]

Disintegration test: The test was employed on six tablets by using tablet disintegration tester (Copley Scientific NE4-COP, Nottingham, UK).The disintegration media of the tester was distilled water maintained at 37ºC.Disintegration time was calculated as the time required for complete breakdown of the tablets into pieces small enough to pass through the screen fixed at the bottom of the 6-tubes basket assembly of the instrument.

Wetting time: The wetting time of the tablets was monitored by using dye method. Filter paper was soaked in 6 ml of distilled water placed in petri- dish. Alurra red powder (dark brown) was carefully sprinkled over the surface of each tablet that was then gently placed on the wet filter paper. The time required for the generation of the red color on the tablet surface was recorded and taken as the wetting time.[24]

In vitro dissolution studies: The dissolution studies were conducted to all tablet batches either intact or after crushing to address concerns of possible variation in drug release pattern if the tablets were either chewed or mistakenly swallowed whole. The experimental conditions were similar to that applied for co-grinded mixtures in the developmental stage (900 ml of phosphate buffer (pH 7.2) kept at 37 ºC±0.5ºC, paddle speed at 50 rpm). The test conducted for 1 hr during which samples were withdrawn at different time intervals and tested for drug concentration by UV spectrophotometric assay at 222 nm.

Statistical analysis

All experiments were performed in triplicates and statistical analysis employed Student's *t*-test. Results were considered significant when P-value is less than 0.05.

RESULTS AND DISCUSSION

FTIR spectroscopy

FTIR spectra of Dexibuprofen, mannitol and meglumine in pure state and their co-processed formulations are shown in (Figure 1). The spectrum of unprocessed Dexibuprofen shows the absorption peaks correspond to its chemical structure. These include the carbonyl absorption band at 1707 cm^{-1}, the peak at 1327 cm^{-1} for the C–O stretching vibrations. The absorption bands at 3085 cm^{-1} is for the OH group, at 946 cm^{-1} for OH out of plane bending, at 2956 cm^{-1} for CH stretching. Absorption band at 1510 cm^{-1} is for C=C and that at 1464 cm^{-1} is for C-C stretching. The recorded spectrum resembles that published for the same drug.[25] Ethanol-assisted wet grinding of Dexibuprofen produced similar spectral pattern to the pure drug. This indicates that the adopted processing technique did not modulate the structure of the drug.

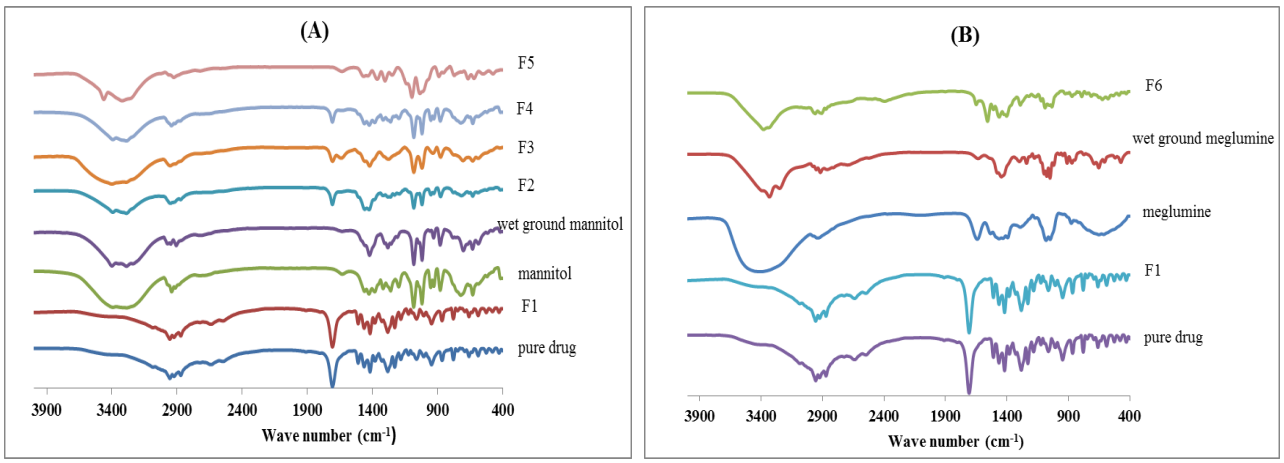

Figure 1: FTIR spectra of unprocessed and processed (F1) drug with either mannitol (A) or meglumine (B) and their co-processed mixtures. Formulations details are in Table 1.

Regarding the FTIR spectra of mannitol, the absorption band of OH stretching vibrations appears at 3393 cm^{-1}. Out of plane and in plane OH bending noticed at 722 and 1427 cm^{-1}, respectively. Peaks at 1083 and 1019 cm^{-1} are attributed to C-O stretching vibrations, while those at 2942 and 2914 cm^{-1} were due to C-H stretching vibration. The spectrum is in agreement with the published spectrum for pure mannitol.[26] For Meglumine, the FTIR spectrum showed stretching vibration peaks of C–O clearly seen at 1047 and 1081 cm^{-1}. Aliphatic C–H appeared at 2942 cm^{-1}. The broad peaks at 3416 and 3398 cm^{-1} were attributed to NH and OH stretching modes. Also NH bending vibration was seen at 1640 cm^{-1}. This relates well with the published spectrum for the meglumine.[27]

Wet grinding of pure mannitol and pure meglumine with ethanol did not result in noticeable variations in FTIR spectrum compared to the unprocessed form. This finding is advantageous as any spectral changes after co-processing of Dexibuprofen and either of mannitol (formulas F2 through F5) or meglumine (F6) will indicate interaction between both materials.

FTIR spectrums of co-grinded drug with mannitol in all ratios kept the main absorption bands of Dexibuprofen and indicated no significant changes compared with the spectrum of the drug with (F1) or without (control) processing (Figure 1A). This indicates no interaction between the drug and mannitol.

For Formula F6 (drug: meglumine 1:1 ratio), the carbonyl group of the drug after wet grinding with meglumine was shifted from 1707 cm^{-1} to 1649 cm^{-1} (Figure 1B). This would indicate possible amide bond formation between OH of carboxylic acid of drug and NH of meglumine.

Differential scanning calorimeter (DSC)

DSC studies were employed to investigate the thermal behavior of Dexibuprofen, excipients and their wet co-grinded mixtures. The obtained thermograms are shown in Figure 2. For each thermal event, the thermokinetic properties expressed as the transition midpoint (Tm), onset, endset as well as the enthalpy were calculated and are listed in Table 3.

The thermogram of unprocessed Dexibuprofen showed three endothermic peaks. The first one was sharp peak having onset of 40ºc, endset of 63.36ºC and Tm of 52.0ºC, and enthalpy of 248.09 J/g (Figure 2, Table 3). This peak corresponds to its melting point and reflects its crystalline nature. The second and third peaks appeared as broad peaks at 217.9ºC and 260.6ºC. These thermal events can be considered as reflection of drug decomposition. This thermal behavior is similar to the previously published spectrum of the same drug.[28] Ethanol-assisted grinded Dexibuprofen produced crystalline product with some modifications in thermal behavior compared to the unprocessed one (Figure 2, Table 3). The melting transition started at 44.3ºC and ended at 57.7ºC with Tm shifted to lower value of 51.4ºC. This was accompanied with large reduction in the enthalpy to 72.04 J/g. The decomposition peaks were modulated after processing becoming weak with a Tm of 184.3ºC and 213.3ºC and with a significant reduction in enthalpies to 29.8J/g and12.18J/g, respectively.

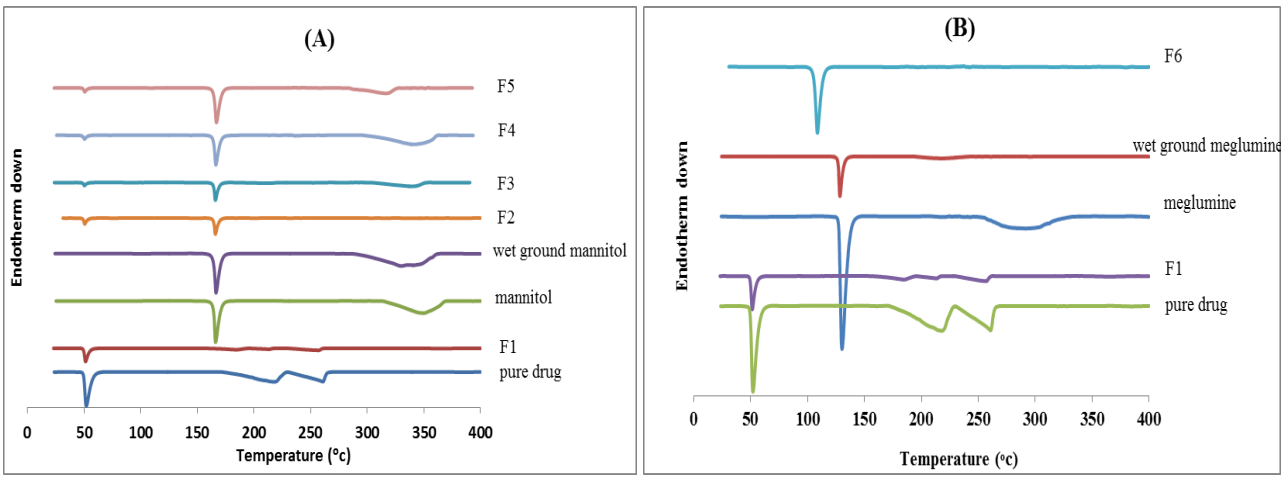

Figure 2: DSC thermograms of unprocessed and processed (F1) drug with either mannitol (A) or meglumine (B) and their co-processed mixtures. Formulations details are in Table 1.

Table 3: The thermodynamic parameters of the drug, additives and wet ground mixtures.

Formulation	Tm (ºC)	Onset(ºC)	Endset(ºC)	Δ H (J/g)
Pure Dexibuprofen				
1st peak	52.02	40	63.36	248.09
2nd peak	217.97	181.11	226.59	360.88
3rd peak	260.66	236.99	264.63	207.53
Mannitol				
1st peak	166.20	153.79	179.41	250.55
2nd peak	349.35	316.56	368.35	467.29
Wet grinded mannitol				
1st peak	166.52	152.54	180.01	251.27
2nd peak	330.10	301.01	361.19	645.92
Meglumine				
1st peak	130.25	118.72	144.15	401.46
2nd peak	291.39	253.83	324.11	281.49
Wet grinded meglumine				
1st peak	128.50	120.68	135.41	73.68
2nd peak	217.79	194.49	242.09	26.23
F1 (positive control)				
1st peak	51.45	44.3	57.76	72.04
2nd peak	184.27	163.2	193.62	29.8
3rd peak	213.39	197.65	217.37	12.18
F2				
1st peak	50.59	47.48	53.84	26.60
2nd peak	165.90	157.47	173.88	75.57
F3				
1st peak	50.36	48.22	53.44	14.3
2nd peak	165.87	156.67	174.78	86.13
3rd peak	338.33	304.70	350.76	129.59
F4				
1st peak	50.42	48.33	53.78	18.23
2nd peak	166.32	153.96	177.67	174.27
3rd peak	341.13	308.63	361.26	412.33
F5				
1st peak	50.62	48.82	53.8	18.21
2nd peak	166.82	154.44	177.68	220.09
3rd peak	316.53	283.44	326.11	159.94
F6	108.67	97.07	119.89	97.73

The DSC spectrum of pure mannitol was characterized by a sharp endothermic peak with a Tm at 166.2ºC (onset of 153.7ºC, endset of 179.4ºC and heat of fusion=250 J/g). In addition, a broad peak was recorded at 349.3ºC reflecting its decomposition at such high temperature. The similar thermogram was report for the same excipient.[29] Recrystallization of mannitol from ethanol followed by wet grinding produced crystalline powder with similar melting point but slight shifting in the decomposition peak to 330.1º C(Figure 2A and Table 3).

Meglumine showed a sharp endothermic peak at 130.2ºC with onset of 118.7ºC, endset of 144.1ºC and having enthalpy of 401J/g. This peak corresponds to melting transition of meglumine. Another broad peak was seen at 291.3ºC starting at 247.8 and ending at about 321.2ºC and taken for its decomposition. This thermogram highlights the crystalline nature of meglumine and is in good agreement with the published thermogram for the same material.[30, 17] Treating meglumine with ethanol followed by grinding modulates its thermal pattern (Figure 2B, Table 3). The melting transition recorded earlier at Tm of 128ºC, the enthalpy was similarly reduced to 73.6J/g. Decomposition endotherm was shifted to lower one that recorded at 217.7ºC with enthalpy reduction to be 26J/g. This may be attributed to particle size reduction.

Preparation of the drug by wet co-grinding produced drug crystals with a thermogram depending on the excipients used in the process. The DSC traces of co–processed drug and mannitol showed slight modification compared to that of the individually processed materials. The thermogram of all formulations showed two distinct endothermic events, the first of which is for the drug with a transition peak of similar values around 50ºC with concomitant reduction in the enthalpy (Figure 2A and Table 3). The second transition peak is attributed to thermal transition of mannitol and appeared as a sharp peak at Tm similar to that of the wet grinded mannitol. It should be highlighted that for F2 (1:1 ratio) no decomposition peak was noted at the temperature range

used. This might indicate formation of new crystalline species or increased intermolecular forces. Increasing mannitol concentration (F3 to F5), broad endothermic peak was detected and its Tm decreases with increasing mannitol concentration. It worth noting that decomposition peaks were reduced for both components in all binary co-ground mixtures. Shifting of the decomposition peak to a lower temperature was previously explained by weakening of in the intermolecular interaction.[31]

Regarding co-processed Dexibuprofen and meglumine, formula F6 resulted in new endothermic peak at 108ºC most probably due to amide formation (Figure 2 B, Table 3). In addition, the new species do not show any degradation endotherm which reflects its relative stability compared to parent compounds. This finding is supported by the infrared spectroscopic findings.

X-ray powder diffraction (PXRD)

The PXRD patterns of the processed (F1) and unprocessed Dexibuprofen, mannitol, meglumine are shown in Figure 3, together with their co-processed formulations (F2 through F6). PXRD is an instrumental technique widely accepted as a tool to confirm or eliminated co-crystal formation.[31,15] The diffractogram of the raw Dexibuprofen indicated its crystalline nature which was shown by multiple characteristic peaks at diffraction 2 theta values of 6.87, 7.41, 12.12, 12.81, 13.38, 13.92, 16.26, 17.79, 18.72, 19.5, 21.81, 21.57, 22.26, 24.33, 26.73, 28.56, 30.36, 31.89, and 36.18. This diffraction pattern is similar to reported data for the same drug.[13] Ethanol assisted re-crystallization of Dexibuprofen (F1) resulted in crystalline product with an X-ray diffraction pattern different from that of unprocessed drug with respect to the intensity of the peaks (Figure 3A). This can suggest reduction in the particle size of the drug after processing in accordance to published data with the same explanation.[32, 33]

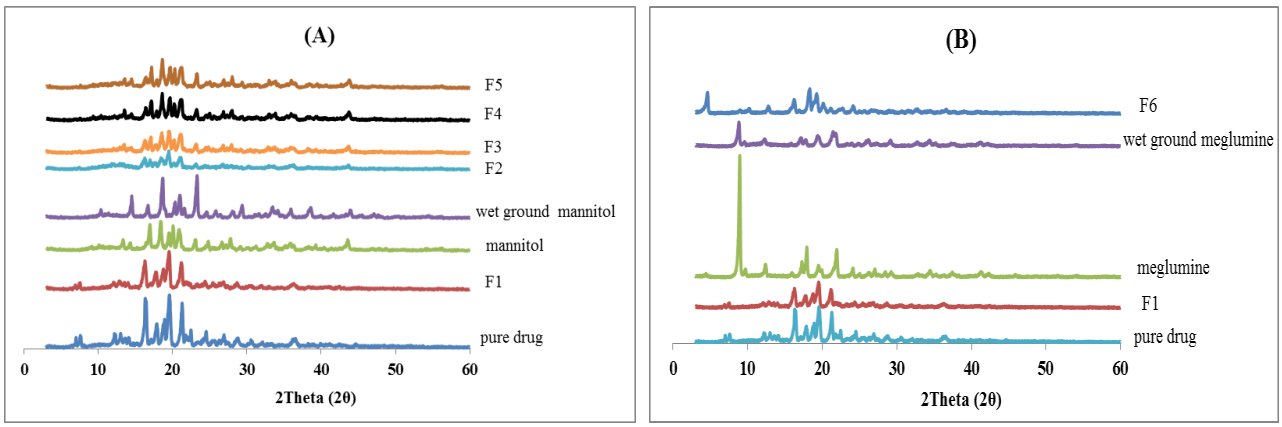

Figure 3: X-ray diffraction pattern of unprocessed and processed (F1) drug with either mannitol (A) or meglumine (B) and their co-processed mixtures. Formulations details are in Table 1.

The crystalline nature of mannitol was signified from their characteristic diffraction pattern (Figure 3A). The figure reflects its diffraction peaks at 2 θ values of 13.14, 14.13, 16.83, 18.33, 19.41, 20.01, 20.7, 22.92, 24.6, 26.49, 27.03, 27.6, 28.92, 33.48, 35.67, 36.15, 39.06, 43.38º. The same pattern was previously recorded for the same substance.[34] Recrystallization of mannitol from its ethanolic solution followed by wet grinding produced crystalline structure with different diffraction compared to the unprocessed form. The new diffractogarm showed new diffraction peaks and alterations in peaks intensities (Figure 3A).These changes in the crystalline structure can be attributed to the solvent of crystallization process. The X-ray diffraction pattern of unprocessed meglumine, showed numerous strong diffraction peaks which correspond to the crystallinity of the material. The peaks were observed at 2θ values of 8.94, 9.51, 12.21, 15.81, 17.19, 17.88, 19.32, 21.84, 23.94, 26.88 28.29, 28.98, 34.26, 37.23, 41.13, 42.15º. Similar diffractogram was reported by other researchers.[30] Processed meglumine showed no differences in the peaks positions with only some reduction in intensity of the peaks and broadening (Figure 3B).

Formulations combing mannitol and Dexibuprofen produced diffractograms with reduced peaks intensities with the detected peaks belonging to mannitol in absence of the principle peaks of Dexibuprofen (Figure 3A). The intensity of the recorded peaks increased with increasing concentration of mannitol. These results suggest at least partial amorphousization of the drug after co-processing with mannitol.

X-ray diffractogarm of co-ground meglumine with drug revealed formation of different diffraction pattern which showed new diffraction peaks at a diffraction angle 2θ of 4.5º, 10.02º, 18.15º and 20.02º (Figure 3B). From the combined instrumental analysis, we can conclude that wet co-grinding of meglumine with Dexibuprofen resulted of formation of new chemical species probably due to amide bond formation.

***In vitro* drug release**

The dissolution profiles of Dexibuprofen from different formulations are presented as percentage drug released against time in Figure 4. Pure drug was used as negative control. Drug crystals prepared by wet grinded of the

pure form alone, after being liberated from its ethanolic solution, was taken as positive control. The dissolution parameters are listed in Table 1 as percentage drug released after 5 minutes (Q5) and dissolution efficiency (DE), the later was computed according to Khan (1975).

Unprocessed drug released 24% of the loaded dose after 5 minutes that was slowly increased with time giving a total dissolution efficiency of 66%. For therapeutic agent like Dexibuprofen, a high initial release is preferable to produce rapid effect. Therefore, the adopted technique was used in a trial to obtain prompt drug release. For positive control (formula F1), there was a significant ($P < 0.05$) increase in Q5 reaching 42%, dissolution efficiency was similarly increased (Table 1). This enhancement is further confirmed by the similarity factor test that was less than 50 %. This improved dissolution parameters could be attributed to the reduced particle size of the drug after recrystallization and grinded. This assumption is supported by the recorded changes in X-ray diffractogram. Possible transformation to the amorphous form, as shown by DSC data, can contribute to such improvement.

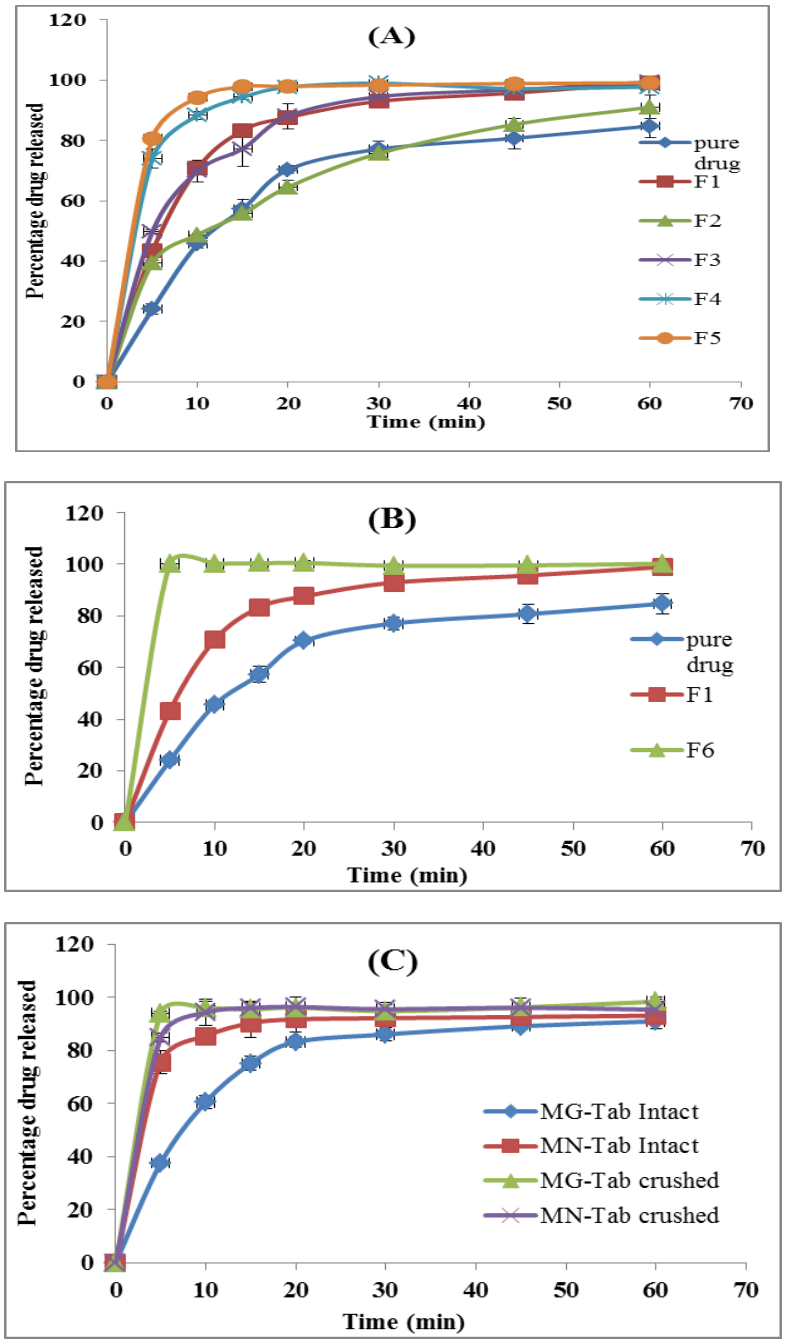

Figure 4: ***In vitro*** **dissolution profiles of Dexibuprofen from its unprocessed form and different formulations prepared using mannitol (A) or meglumine (B), together with dissolution from intact and crushed tablets (C). For detailed formulations refer to Tables 1 and 2.**

Our original aim was to enhance Dexibuprofen dissolution using co-crystal strategy. At the stage of experimental design mannitol was selected as potential co-crystal coformer for Dexibuprofen based on the fact that it was successively used as conformer for hydrochlorothiazide.[35] In addition to its sweet taste and cooling effect, mannitol is known to be inert excipient for both the therapeutic agent and the patient's body. It also reported that mannitol has good compactibility and the ability to produce strong tablets.[36] Co-grinded formulations prepared using mannitol improved dissolution parameters compared to control ($P<0.05$), the extent of which depended on the relative ratio of mannitol. Equimolar ratio of drug and mannitol (F2) did not show significant improvement in drug dissolution over positive control (F1). These results were also confirmed from similarity factor where the value of f_2 was more than 50. It should be noted that *f2* values greater than 50 ensure absence of significant difference between formulation F2 and positive control. This reflects that low concentration of mannitol is not enough to enhance the dissolution rate. This coincides with the DSC data that suggested increased intermolecular interaction that may slow down drug liberation from the mixture.

For other co-grinded mixtures, the dissolution behavior depended on the molar ratio of both components. As the concentration of mannitol increased, the dissolution parameters of Dexibuprofen increased accordingly (Figure 4A). Formulations F3, F4 and F5 showed Q5 of about 50%, 74% and 81%, respectively. The dissolution efficiency increased in the same order (Table 1). Similarity factor of values less than 50 indicates significant improvement compared to both unprocessed and processed drug. As possible co-crystal formation was eliminated by the results of the performed instrumental analysis techniques, the obtained improvement could be attributed to reduced particle size as suggested by X-ray powder diffraction data. Particle size has a direct effect on dissolution rate of pharmaceutical compounds as stated by Noyes-Whitney equation.[37] The improved dissolution could be also due to possible changes in crystal lattice by formation of crystals having lower intermolecular forces, as evidenced by the slight decrease in transition temperature and heat of fusion (see DSC data). Another important factor is the adsorption of the drug microparticles onto the surface of mannitol.

For drug-meglumine co-processed mixture (F6), a marked increase in the initial drug release approaching 100% dissolution after first five minutes (Figure 4B). This can be due to the transformation of Dexibuprofen to the salt form by interacting with the amine group in meglumine. Salt formation due to meglumine was reported for other Class II drugs.[38] The results of FTIR and X-ray powder diffraction confirm our supposition of salt formation. It worth noting that drug solubility is also expected to increase accordingly.

Characterization of Chewable tablets

Pre-compression studies

In the present study, powder flowability was quantified using the traditional angle of repose and the tapped density techniques. These flowability indicators were selected as each method represents a specific state of the powder blend generally found during tablet manufacturing. Angle of repose usually predicts how easily particles roll over one another during pouring to ensure that powder flow occurs in an un-interrupted state from the hopper to the die cavities of the tablet press The more the co-adhesive the powder, the higher the angle of repose. The results shown in Table 4 indicate that the two powder blends have values ranged from 28 to 31º with no difference between different formulations, suggesting good flowability.[39]

Hausner ratio (HR) is considered as a straightforward and convenient way to reflect how well the particles in powder bed packed together during tableting. It is the ratio of tapped density to loose poured bulk density. Values of more than 1.5 considered of bad flow due to highly packed structures. The results in Table 4 reflect suitability of powder blends for tableting process. For Carr's index, materials having Carr index values more than 20 to 25 % are classified as non-free-flowing.[39] Therefore, powder blends considered acceptable (Table 4).

Quality attributes of the tablets

Chewable tablets were prepared according to Master Formula shown in Table 2. Mannitol-based (MN-Tab) and Meglumine-based (MG-Tab) tablets were prepared using co-grinded mixtures F3 and F6, respectively. All tables were acceptable regarding quality attributes stated by the US Pharmacopeia.[23] For weight variation test, the deviation from the mean weight being less than 1% indicating uniformity of weight due to good flowability of the powder blends. Drug content was found to be 99.8 and 97.3 for MN-Tab and MG-Tab, respectively.

Table 4: Results of powder flowability, quality control studies and *in vitro* dissolution parameters for crushed and intact tablets.

	Powder flowability			Friability (%)	Disintegration Time (min)	Intact Tablets		Crushed Tablets	
	Angle of repose	Hausner ratio	Carr's index			Q5 (%)	DE(%)	Q5 (%)	DE(%)
Mannitol Tab	28.8 ± 2.3	1.2 ± 0.02	16.8 ± 1.3	1.0	0.22	75.5± 4	86.4±3	84.9±2	90.9 ± 3
Meglumine Tab	31.3 ± 1.1	1.25 ± 0.02	20.2 ± 1.4	0.2	3.9	37.5± 3	76.5± 1	94.0±1	92.0 ± 2

- Q5 is percentage amount released after 5 minutes
- DE is the dissolution efficiency

MG-Tabs were more resistant to friability with longer wetting time compared to MN-Tab. Though there is no pharmacopeial specification for chewable tablets regarding disintegration time, the International pharmacopeia recommends the test to address concerns that may arise if such tablets were swallowed whole without pre-crushing in the mouth. All tablets showed acceptable disintegration time, though that for MG-Tab was longer (Table 4). This relatively longer time could be attributed to binding effect of meglumine.

The *in vitro* drug dissolution studies were performed using crushed as well as intact tablets. The latter was to evaluate drug release if tablets were mistakenly swallowed whole. The dissolution profiles of Dexibuprofen from tablets are presented in Figure 4C. Dissolusion data (Q5 and DE%) are in Table 4. For MN-Tab, intact tablets released 75.5% of the labeled drug in the first five minutes, while tablet granules, due to crushing, released 85% of Dexibuprofen that was statistically higher than that for intact one ($P<0.05$). Nevertheless, the total dissolution efficiencies were similar ($P>0.05$). It is interesting to note that co-grinded F3 mixture alone showed an initial release of only 49% of the drug that was significant increased when incorporated in tablets taken tested either intact or crushed. Such enhancement could be due to the adsorption of the drug over excipients used with subsequent rapid dispersion. Similar findings were previously reported and were similarly explained.[32]

For MG-Tab, crushed tablets showed dissolution parameters of 94 and 92% for Q5 and %DE, respectively. Comparing this dissolution pattern with that recorded with the corresponding co-grind mixture, no significant difference can be recorded. This indicates that crushing of the tablets eliminated the effect of compression and chewing will ensure immediate release of the drug. On the other hand, for intact MG-Tab a surprisingly reduction in Q5 reaching 37% was noted. Dissolution efficiency was similarly reduced to 76.5%. Such retardation of drug dissolution coincides with the recorded long disintegration time (Table 4). This could be attributed to meglumine in the powder. Meglumine is a derivative of sorbitol that is reported to have binding ability.[40] Therefore, there is a high probability that it imparted cohesiveness to tablets during compaction.

CONCLUSION

The objective of this work was to enhance Dexibuprofen dissolution and formulate chewable tablets. The study used mannitol and meglumine as promising excipients for enhancing dissolution rate of Dexibuprofen after ethanol assisted co-grinding. Both excipients improved Dexibuprofen dissolution rate. Solid state characterization for the obtained formulations indicated reduced crystalline structure of the drug, but did not confirm co-crystal formation. For meglumine-containing mixtures, salt formation was suggested. The co-ground mixtures showed best dissolution parameters were successfully formulated into chewable tablets which liberate the labeled drug immediately after chewing. Mannitol based tablets showed fast release of Dexibuprofen from intact as well as crushed tablets. Meglumine based tablets have to be chewed for fast drug release due to retarded disintegration rate which results from the binding effect of meglumine.

REFERENCES

1. Krishnaiah YS. Pharmaceutical technologies for enhancing oral bioavailability of poorly soluble drugs. J Bioequiv Availab, 2010; 2(2): 28–36.
2. Seager H. Drug-delivery Products and the Zydis Fast-dissolving Dosage Form. J pharm Pharmacol, 1998; 50(4): 375-82.
3. Lipinski C. Poor aqueous solubility–an industry wide problem in drug discovery. Am Pharm Rev, 2002; 5(3): 82–5.
4. Kathiresan K, Vijin P, Moorthi C, Manavalan R. Formulation and evaluation of loratadine chewable tablets. Res J Pharm Bio Chem Sci, 2010; 1(4): 763-74.
5. Patel Y, Shukla A, Saini V, Shrimal N, Sharma P. Chewing Gum as a drug delivery system. Int J Pharm Sci Res, 2011; 2(4): 748.
6. Shoukri RA, Ahmed IS, Shamaa RN. In vitro and in vivo evaluation of nimesulide lyophilized orally disintegrating tablets. Eur J Pharm Biopharm, 2009; 73(1): 162–71.
7. Hardikar MS. Chiral non-steroidal anti-inflammatory drugs--a review. J Indian Med Assoc, 2008; 106 (9): 615-8, 622-24.
8. El-Houssieny BM, ZinEldin E, El-Messiry HM. Enhancement of solubility of dexibuprofen applying mixed hydrotropic solubilization technique. DD & T, 2014; 8(4): 178-184.
9. Kaehler S, Phleps W, Hesse E. Dexibuprofen: pharmacology, therapeutic uses and safety. Inflammopharmacology, 2003; 11(4-6):371–83.
10. Di Pierro F, Settembre R. Safety and efficacy of an add-on therapy with curcumin phytosome and piperine and/or lipoic acid in subjects with a diagnosis of peripheral neuropathy treated with dexibuprofen. J Pain Res, 2013; 6:497-503.
11. Adams SS, Bresloff P, Mason CG. Pharmacological differences between the optical isomers of ibuprofen evidence for metabolic inversion of the (-) isomer. J Pharm Pharmacol, 1976; 28(3): 256-57.
12. Bonabello A, Galmozzi MR, Canaparo R, Isaia GC, Serpe L, Muntoni E, Zara GP. Dexibuprofen (S(+)-Isomer Ibuprofen) reduces gastric damage and improves analgesic anti-inflammatory effects in rodents. Anesth Analg, 2003; 97(2): 402-8.
13. Abdelbary G, Makhlouf A. Adoption of polymeric micelles to enhance the oral bioavailability of dexibuprofen: formulation, in-vitro evaluation and in-vivo pharmacokinetic study in healthy human volunteers. Pharm Dev Technol, 2014; 19(6): 717-27.

14. Elagamy HI, Essa EA, El Maghraby GM, Nouh A. Preparation and evaluation of chewable tablets of naftopidil. Drug dev Ind Pharm. 2019; 45(10): 1695–1706.
15. Essa EA, Elbasuony AR, Abdelaziz AE, El Maghraby GM. Co-crystallization for enhanced dissolution rate of bicalutamide: Preparation and evaluation of rapidly disintegrating tablets. Drug Dev Ind Pharm, 2019; 1-32.
16. Walsh D, Serrano DR, Worku ZA, Norrisa BA, Healy AM. Production of cocrystals in an excipient matrix by spray drying. Int J Pharm, 2018; 536: 467–477.
17. Hussien MA, Essa EA, El Gizawy SA. Investigation of the effect of formulation additives on telmisartan dissolution rate: development of oral disintegrating tablets. EJBPS, 2019; 6(4): 12-20.
18. Essa EA, Elkotb FE, ZinEldin E, El Maghraby GM. Development and evaluation of glibenclamide floating tablet with optimum release. Drug Del Sci Tech, 2015; 27: 28-36.
19. Shan N, Toda F, Jones W. Mechanochemistry and co-crystal formation: effect of solvent on reaction kinetics. Chem Commun, 2002; 20: 2372-73.
20. Khan KA. The concept of dissolution efficiency. J Pharm Pharmacol, 1975; 27(1): 48-9.
21. Moore JW, Flanner HH. Mathematical Comparison of Dissolution Profiles. Pharm Tecnol, 1996; 20: 64-74.
22. Sinko PJ. Martin's Physical Pharmacy and Pharmaceutical Sciences. Philadelphia, PA, USA: Publisher and Distributor, 2006.
23. United States Pharmacopiae National Formulary 24. Rockville (MD): United States Pharmacopial Convention; 2000.
24. Jain CP, Naruka PS. Formulation and evaluation of fast dissolving tablets of valsartan. Int J Pharm and Pharm Sci, 2009; 1(1): 219-26.
25. Rajesh K, Nair R, Rajalakshmi R, Latha P. Arun kumar KS, Nama V. Inclusion complex of dexibuprofen and its in-vitro and in-vivo evaluation. Int Bio Pharm Res, 2011; 2: 34-8.
26. Katara R, Majumdar DK. Eudragit RL 100-based nanoparticulate system of aceclofenac for ocular delivery. Colloids Surf B, 2013; 103: 455-62.
27. Moradi L, Zare M. Ultrasound-promoted green synthesis of 1, 4-dihydropyridines using fuctionalized MWCNTs as a highly efficient heterogeneous catalyst. Green Chem Lett Rev, 2018; 11(3): 197-208.
28. Kim SR, Kim JK, Park JS, Kim CK. Dry elixir formulations of dexibuprofen for controlled release and enhanced oral bioavailability. Int J Pharm, 2011; 404(1-2): 301-7.
29. Jaipal A, Pandey MM, Charde SY, Raut PP, Prasanth KV, Prasad RG. Effect of HPMC and mannitol on drug release and bioadhesion behavior of buccal discs of buspirone hydrochloride: In-vitro and in-vivo pharmacokinetic studies. Saudi Pharm J, 2015; 23(3): 315-26.
30. Zhu Z, Yang T, Zhao Y, Gao N, Leng D, Ding P. A simple method to improve the dissolution of repaglinide and exploration of its mechanism. Asian J pharm sci, 2014; 9(4): 218-25.
31. Abdelquader MM, Essa EA, El Maghraby GM. Inhibition of Co-Crystallization of Olmesartan Medoxomil and Hydrochlorothiazide for Enhanced Dissolution Rate in Their Fixed Dose Combination. AAPS Pharm Sci Tech, 2019; 20(1): 3-12.
32. Essa E, Elmarakby AO, Donia AM, El Maghraby GM. Controlled precipitation for enhanced dissolution rate of flurbiprofen: development of rapidly disintegrating tablets. Drug Dev Ind Pharm, 2017; 43(9): 1430-39.
33. Essa E, Negm M, ZinEldin E, El Maghraby G. Fast disintegrating tablets of amiodarone for intra-oral administration. J App Pharm Sci, 2017; 7(01): 064-072.
34. Yadav PS, Kumar V, Singh UP, Bhat HR, Mazumder B. Physicochemical characterization and in vitro dissolution studies of solid dispersions of ketoprofen with PVP K30 and d-mannitol. Saudi Pharm J, 2013; 21(1): 77-84.
35. Rodrigues M, Lopes J, Sarraguça M. Vibrational Spectroscopy for Cocrystals Screening.A Comparative Study. Molecules, 2018; 23(12): 3263-78.
36. Leonhard Ohrem H, Schornick E, Kalivoda A, Ognibene R. Why is mannitol becoming more and more popular as a pharmaceutical excipient in solid dosage forms? Pharm Dev Technol, 2014; 19(3): 257-62.
37. Noyes AA, Whitney WR. The rate of solution of solid substances in their own solutions. J Am Chem Soc, 1897; 19(12): 930–4.
38. Zhong L, Zhu X, Yu B, Su W. Influence of alkalizers on dissolution properties of telmisartan in solid dispersions prepared by cogrinding. Drug Dev Ind Pharm, 2014; 40(12): 1660-9.
39. Carr R L. Evaluating flow properties of solids. Chem Eng, 1965; 72(2): 163-69.
40. Shailendra P, Shikha A, Singh LB. Natural binding agents in tablet formulation. Int J Pharm Biol Arch, 2012; 3(3): 466-73.