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Research Article

STUDYING THE RELEASE OF DICLOFENAC SODIUM FROM GLYCERIDES

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ABSTRACT

Objective: To compare the retarding effect of the glycerides waxy matrices on diclofenac sodium which was selected as a model drug?

Methods: The mixture of drug with different glycerides waxy matrices were prepared by either physical mixing or melt granulation technique. Different methods of analysis like IR and powder x-ray diffraction were carried out in addition to the drug release from different matrices.

Results: The compressibility index and Hausner's ratio show excellent flow characteristics . The tablets show a low friability %. The waxy matrices improve the hardness and tensile strength of the tablet. The waxy material promotes a greater plastic deformation of the particles during compaction. The plastic deformation leads to an increase in the area of particle-particle contact and cohesion further leading to the formation of hard tablets. The dissolution rate of drug from physical mixture matrices of compritol and precirol WL is markedly higher than that from precirol ATO5 with also markedly burst effect. The dissolution profile consists of two phases. The dissolution rate of drug from matrices prepared from melted bases can be arranged in the following order from compritol > precirol WL > precirol ATO5 without any rapid initial drug release. FTIR studies ruled out the possibility of chemical interaction and complex formation between diclofenac sodium and glycerides used and prepared by either as physical mixture or by melting. X-ray diffraction shows the crystlinety of the drug in all physical mixtures with glycerides. There is no evidence of drug crystal peaks with compritol and prepared by melting suggesting that diclofenac is in either amorphous form or molecularly dispersion. The mixtures which are prepared with either precirol WL or ATO 5 and melted granulation showed two forms of drug, one crystalline form and the other in non crystalline one. Different semi-empirical kinetic equations were applied to interpret the release rate from different matrix system in correlation to the suggested entrapment method of drug according to the different method of analysis.

Conclusion: This study shows that glycerides waxy matrices have strong retarding effect of the drug release even when the drug is highly water soluble like diclofenace sodium.

Keywords: Compritol, Precirol LW, Precirol ATO 5, Diclofenac Sodium, Drug release.

INTRODUCTION

Tablet matrix system containing hydrophobic lipid based materials have been widely used in formulations for controlled drug delivery applications because of their chemical inertness [1], cost effectiveness, regulatory acceptance and above all flexibility to achieve the desired drug release profile [2] These are widely used as release retardants in the design of sustained release tablets, suspensions, beads, implants, and microcapsules.

Such materials also provide several advantages ranging from good stability of varying pH values and moisture levels to well establish safe application in humans [3].

Glycerides are a family of excipients which have generated considerable interest for the preparation of oral dosage forms. They are a wide range of meltable excipients, which are composed of mixtures of glycerides and fatty acid esters of polyethylene glycol (PEG) [4]. The nature and the proportion of these components determine the hydrophilic–lipophilic characteristic (HLB value) of these excipients and the drug release properties from the corresponding dosage forms [5, 6].

Some glycerides such as glyceryl mono stearate (precirol WL2155), glyceryl palmitostearate (Precirol ATO 5) and Glyceryl behenate (Compritol 888 ATO) can be used for the preparation of sustained release dosage forms. The esterification of glycerol by long chain fatty acid gives them a pronounced hydrophobic character with a low HLB value. Glyceryl behenate (Compritol 888 ATO) is a waxy material, originally introduced as a lubricant in compressing tablets, which has recently had a wide application as a sustained-release agent. It is commonly used as a lubricant and binding agent for tablets in the concentration of 1-3% and a sustained release excipients in concentrations above 10%. A recent study by Barthelemy and coworkers investigated that use of glyceryl behenate as a hot melt coating agent to prolong the release of theophylline [3].

Precirol ATO5 (glyceryl palmitostearate) is classically used as a lipid vehicle for sustained release formulation [7-8]. The excipient is composed of mono-,di- and triglycerides of palmitic acid (C16) and stearic acid (C18), with a HPL value of 2, a drop point ranging from 52 to 55[7] and acid value is ranging from 200-210 [9].

The use of precirol ATO5 by capsule molding can lead sometimes to a drug release too slow due to high hydrophobicity. Some hydrophilic excipients were already added to precirol ATO5 in order to adjust the drug release from the matrix systems or to solubilize the drug into the matrix system such as mannitol, hydroxypropylmethylcelluose or polxamers [7].

Glyceryl monostearate, a wax like solid in the form of beads, flakes, or powder, is used as a lubricant for tablet manufacturing and may be used to form sustained-release matrices for solid dosage forms [10-11].

Inerbir et al prepared matrices containing 25 % of the release retarding material. The author found that compritol and eudragit imparted strongest retarding effect on the release of etoricoxib, whereas GMS could not impart a significant sustaining effect on the drug release. The higher extent of release in case of GMS could be attributed to its surface- active property (HLB value 3.8) [12].

Melt granulation has been successfully applied to develop sustained release formulations, taste masked formulations with lipophillic melting binders, such as glycerol monostearate, a combination of a hydrophobic materials, a starch derivative and Stearic acid among others [13-16].

Melt granulation is a solvent-free process which involves the use of a substance that melts at a relatively low temperature. This substance can be added in the molten form over the substrate or in the solid form, which is then heated above its melting point. The substance acts as a liquid binding agent, and the technique does not require the use of organic solvents. Moreover, in melt granulation drying is not necessary and thus, the process is less consuming in terms of time and energy compared to other methods [3].

Diclofenac sodium is a potent nonsteroidal anti-inflammatory drug which has anti-inflammatory, analgesic and antipyretic properties. It is used for the treatment of degenerative joint diseases such as

rheumatoid arthritis, osteoarteritis, and ankylosing spondilitis. Diclofenac sodium is rapidly dissolved in intestinal fluid and reaches its maximum blood concentration (C_{max}) within 30 min and is metabolized mainly by hepatic hydroxylation and subsequent conjugation [17]. Diclofenac sodium is freely soluble in water and in order to diminish diclofenac sodium gastrointestinal irritation, which is a common problem with all nonsteroidal anti-inflammatory agents, effective enteric-coated dosage forms have been developed. Accordingly diclofenac sodium was selected as a model drug to compare the retarding effect of the waxy matrix used.

MATERIALS AND METHODS

Materials

Glyceryl behenate (Compritol®888ATO)Gattffosse, France), Glyceryl stearate (Precirol®ATO 5, Gattffosse, France), Glyceryl monostearate(Precirol®WL, Capmul-Abitee group). Diclofenac sodium, (CID pharmaceutical company, Egypt). All other reagent used in this study were of analytical grade and used as received.

Methods

Preparation of matrices

The selected fatty bases (Compritol, Precirol WL or Precirol ATO 5) were melted with continuous stirring in a porcelain dish on a water bath maintained at 75 C. Diclofenac sodium was then added gradually while stirring. The drug-waxy base ratio was 4:1. The mixture was allowed to cool slowly while stirring. The conjugated mass was ground and screened and the granules retained on 1.25 mm sieve were used. The product prepared by this method called melt granulation product. Physical mixtures were also prepared using the same procedure above without heating.

Physical characterization of the prepared mixtures

Angle of repose[3]

The angle of repose of granules was determined by the funnel method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the granules. The granules were allowed to flow through funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation (1).

$$\theta = \tan^{-1} (h/r) \quad (1)$$

Where, θ = angle of repose h = height of cone, r = radius of the cone base

Bulk density[3]

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of 10 gm of powder from each product was introduced into 100 ml measuring cylinder. After that the initial volume was noted and the cylinder was allowed to fall under its own weight on to a hard surface from the height of 2.5 cm at second intervals. Tapping was continued until no further change in volume was noted. LBD and TDB were calculated using the following equations 2 and 3 respectively.

LBD = (weight of powder blend / untapped volume of packing)(2)

TBD = (weight of powder blend / taped volume of packing)(3)

Compressibility Index[3]

The Compressibility Index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the LBD and TBD of a powder and the rate at which it packed down. Carr's Index was calculated using the formula (4):

Carr's Index = (TBD – LBD) × 100(4)

Where, TBD= Tapped bulk density LBD= Loose bulk density

Hausner's Ratio[3]

Hausner's Ratio is the ratio of bulk volume to tapped volume or tapped density to bulk density and calculated by following formula (5).

Hausner's Ratio = V_0 / V (5)

Where, V_0 = Bulk volumeV= Tapped Volume

Drug – excipients interaction

FTIR spectroscopy study

FTIR spectra for drug and drug excipents mixture (physical and melted) were recorded using FTIR Tensor 27 Broker, Germany. Scanning range was 500 to 4000 cm–1 and the resolution was 4 cm^{-1}.

Powder X-ray diffraction

Powder x-ray diffraction patterns of diclofenac sodium and either compritol, precirol WL and precirol ATO 5 physical mixture or melted were investigated using powder X-ray diffractometer (Phillips PW1840). The x-ray was Ni-filtered CuKα 1 radiation with 40 kV and 30 mA over range 4-80/2ɵ.

Post compression evaluation

Thickness[3]

Thickness of tablets was determined using Vanier caliper. Five tablets from each preparation were used and the average values were calculated. The thickness was measured by placing the tablet between the two arms of Vanier calipers.

Hardness[3]

The hardness of five tablets from each preparation was determined using erweka hardness tester. The values of 10 tablets were noted in kg/cm^2.

Friability[3]

The friability of tablets from each preparation was measured using erweka friability tester. Tablets of known weight (W_o) are deduced in a drum for a fixed time and fixed rpm and then weighted again (W). The percentage of friability was calculated from the loss in weight as the following formula (6):

Friability % = [(W_o – W) / W_o] × 100(6)

Tensile Strength[18]

The tensile strength (T) of tablet which is a measure of the stress necessary to cause diametral fracture of the compact was determined from the mean data obtained from the hardness test carried out on the tablets (n = 10) using erweka hardness tester. The T values were calculated from equation below (7):

T = (2P) / (πDt)(7)

Where P is the load applied on the tablet that causes tensile fracture of the tablet of diameter, D, and t is the tablet thickness.

Dissolution rate study

The dissolution rate of diclofenac sodium from tablets of different formulations was studies using USP 22 dissolution apparatus. The dissolution media was 900 ml phosphate buffer pH 6.8 heated 37° ± 0.5 and rotated at 50 rpm. 5 ml samples were withdrawn periodically over the dissolution time of 8 hours and assayed spectrophotometrically at 276 nm. After each sampling equal volume of fresh media solution with the same temperature was replaced. All experiment was carried out in triplicate.

Kinetics of drug release

To determine the value of the regression coefficient (r^2) and mechanism of drug release form different formulations, the cumulative release data were fitted to models. The models applied were zero-order (Cumulative percentage drug released v/s time), first-order (log cumulative percentage drug retained v/s time), Higuchi's square root of time (Cumulative percentage drug released v/s square root of time) and Korsemeyer-peppas double log plot (log of fraction of drug released v/s log time) and Hixon-crowell cube root law (cube root of drug % remaining in matrix vs. time).

$M_t = M_0 + k_0 t$(8)

$\text{Log } M_t = \text{Log } M_0 + k_1 t$(9)

$M_t = M_0 + k_H t^{½}$(10)

$M_t / M_0 = k t^n$(11)

$M_0^{1/3} - M_t^{1/3} = K_{HC} t$(12)

Where M_t is the cumulative amount of drug released at any time, t and M_0 is the dose of the drug incorporated in the delivery system. k_0, k_1, k_H and K_{HC} are rate constants for zero-order, first order, Higuchi models and Hixon-Crowel Cub Root equation, respectively.

RESULTS AND DISCUSSIONS

The selected waxy matrices of diclofenac sodium were prepared with fusion method because this method does not need solvent or water, since the molten wax acts like a binder. The intense of heat, mixing and also the time of mixing were similar during preparation. The physical mixtures were also applied by the same method without applying of heat.

The evaluation of each granules prepared by either physical mixing or applied heat are summarized in table (1). In process quality control parameters (Angle of repose, Loose bulk density (LBD), Tapped bulk density (TBD), Carr˙s index and Haunsr'ratio) were evaluated for the flow properties and the compressibility of granules. From table 1, it can be noticed that, the angle of repose for the physical mixtures granules is very high compared to that other granules prepared by melting the waxy matrices (Melt granulation). The angle of repose is a characteristic of internal friction or cohesion of particles. If the value of angle of repose is high, the powder is cohesive and if the angle of repose value is low, the powder is non cohesive [3]. From the above it can be concluded that the waxy matrices in the physical mixtures increase the cohesion of the powder but not in case of granules prepared by melting method. That is may be due to the higher distribution of the waxy substance in the matrix when is melted.

Table 1: In process quality control parameters of granules

Name of mixture	Angel of repose	LBD (g/cm3)	TBD (g/cm3)	Carr˙s index (%)	Hausner˙s Ratio%
compritol/voltaren Phy.mix.	38.66	1.11	1.250	11.11	0.89
precirol wl/voltren Phy.mix.	35.54	0.94	1.163	18.87	0.81
precirol ato/voltren Phy.mix.	39.81	0.98	1.250	21.57	0.78
compritol/voltaren melting.	26.57	0.52	0.568	9.28	0.91
precirol wl/voltren melting	24.44	0.59	0.625	5.88	0.94
precirol ATO/voltren melting	27.76	0.53	0.581	9.47	0.91

From the same table it can be noticed that, the compressibility index of physical mixture matrices (11.11% - 21%) is higher than that prepared by melting method (5.88% – 9.47%). In addition , The Hausner's ratios for all tested matrices prepared by either method are nearly equal with range between (0.78 – 0.94). Amrutkar et [19], stated that the value of compressibility index below 15% indicates a powder which usually gives rise to excellent flow characteristics , whereas above 25% indicate poor flowability. Lower Hausner's ratio (< 1.25) indicates better flow properties than higher ones (> 1.25). Mehulkumar et [3], found that the Hausner's ratio between 0.87 – 0.94 and stated that, this indicates that all formulation having excellent flow property.

Table 2: Physical parameters tests for different tablets of different matrices:

Name of mixture	Thickness mm	Friability %	Hardness (kg/m²)	Tensile strength(MN/m²)
Compritol/voltaren ph.mix.	3.67	0.71	5.380	0.16
Precirol WL/voltaren ph.mix	3.58	0.65	4.880	0.15
precirol Ato/voltaren ph.mix.	3.47	0.59	3.200	0.10
Compritol/voltaren melted	3.60	0.48	5.000	0.15
precirol WL/voltaren melted	3.48	0.52	3.380	0.10
precirol ATO/voltaren melted	3.44	0.50	3.900	0.12

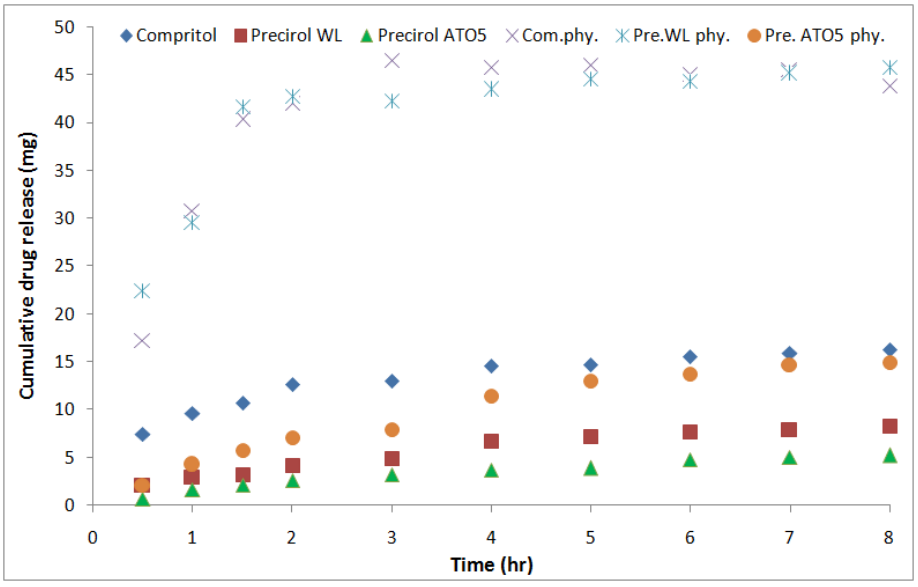


Fig. 1: Drug release from tablets prepared from physical mixture and melted base matrices

The prepared tablets were evaluated for various physical parameters tests. Table (2) shows the physical parameters (thickness, friability %, hardness, and tensile strength) for each mixture. From the table it can be noticed the, there is no change in the prepared tablet thickness. Since the tablets of each mixture have the same diameter which may due to use the same compression set, the same amount of granules and compressed under the same compression force, it can be concluded that, granules and powder blends were consistent in particle size and uniform behavior during compression process.

Friability is an important factor in tablet formulation to insure that the tablet can stay intact and withhold its form any outside form of pressure. The amount of hydrophobic material was found to have a significant effect on friability, hardness and tensile strength of the prepared tablet [18]. The tablets show a low friability % Table 2. The hardness and tensile strength values are also presented in the table. Uhumwangho et al [20], studies the mechanism by which the waxy matrices improve the hardness and tensile strength of the tablet and stated that, the waxy material promote a greater plastic deformation of the particles during compaction. The plastic deformation leads to an increase in the area of particle-particle contact and cohesion further leading to the formation of hard tablets.

Dissolution profile of diclofenac sodium from different tablets prepared from different matrices was studied. Figures 1, represents the dissolution rate of drug from physical mixture tablet and melted base tablets.

From figure 1, it can be noticed that, the dissolution rate of drug from physical mixture matrices of compritol and precirol WL is markedly higher than that from precirol ATO5 with also markedly burst effect. The dissolution profile consists of two phases. The dissolution rate of drug from matrices prepared from melted bases can be arranged in the following order from compritol > precirol WL > precirol ATO5 without rapid initial drug release. The initial burst release from compritol physical mixture and precirol physical mixture could be probably attributed to the dissolution of drug from the surface of the dispersions, indicating failure of formation of dispersion [21].

Mehulkumar et al [3] found that the release of drug from compritol is more retardant than that from precirol ATO5 (which is not in agreeing with this study). The author stated that , among the lipophilic agents, compritol was found to be especially effective for several reasons : its high melting point (65 to 77 ˚C) avoids occurrence of sticking to punches during tabletting operation, it allows for maintenance of tablet integrity even after complete dissolution of drug and release of drug can be easily modulated by varying its concentration in the matrix tablet. At the same time, Özyazici et al, stated that, the higher release rate of metronidazol from compritol matrix if compared with that from precirol ATO5 (which is in agree with this study) may be the result of it being a nonionic surfactant, because it was assumed that the presence of a surfactant increases the wettability of the particles in an aqueous dissolution system [22].

It can be also noticed that, there is a markedly decrease in the total amount of drug release during 8 hours dissolution process. The total amount of drug release from matrices prepared from compritol physical mixture and preccirol WL physical mixture are markedly higher than that from other matrices.

From the same figure, it is completely clear the effect of preparation technique on the drug release. The matrices were prepared by physical mixtures and melt granulation. As a general, the rate and amount of drug release from tablet prepared from melted matrices are extreme lower than that from physical mixture tablets [22, 23].

The initial burst release of the drug from the hydrophobic system is often therapeutically undesirable because the total amount of drug released is markedly influenced by this initial control of release from the dosage form (24). The presence of the burst release for all the polymers being studied clearly indicates that hydrophobic materials at 25% level were not sufficient to produce a desirable pharmacokinetic profile [18].

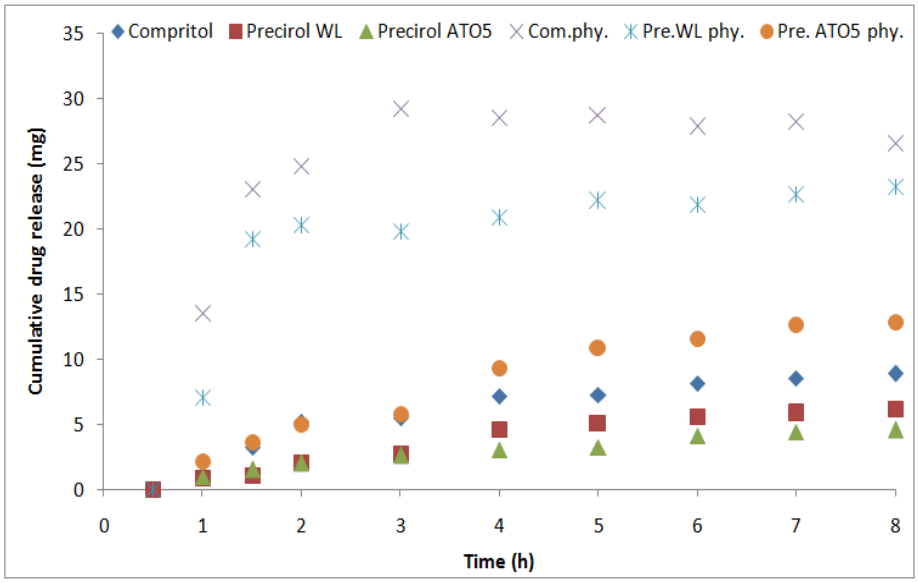


Fig. 2: Drug release from tablets prepared from physical mixture and molted base matrices after subtraction the amount of drug release after half an hour.

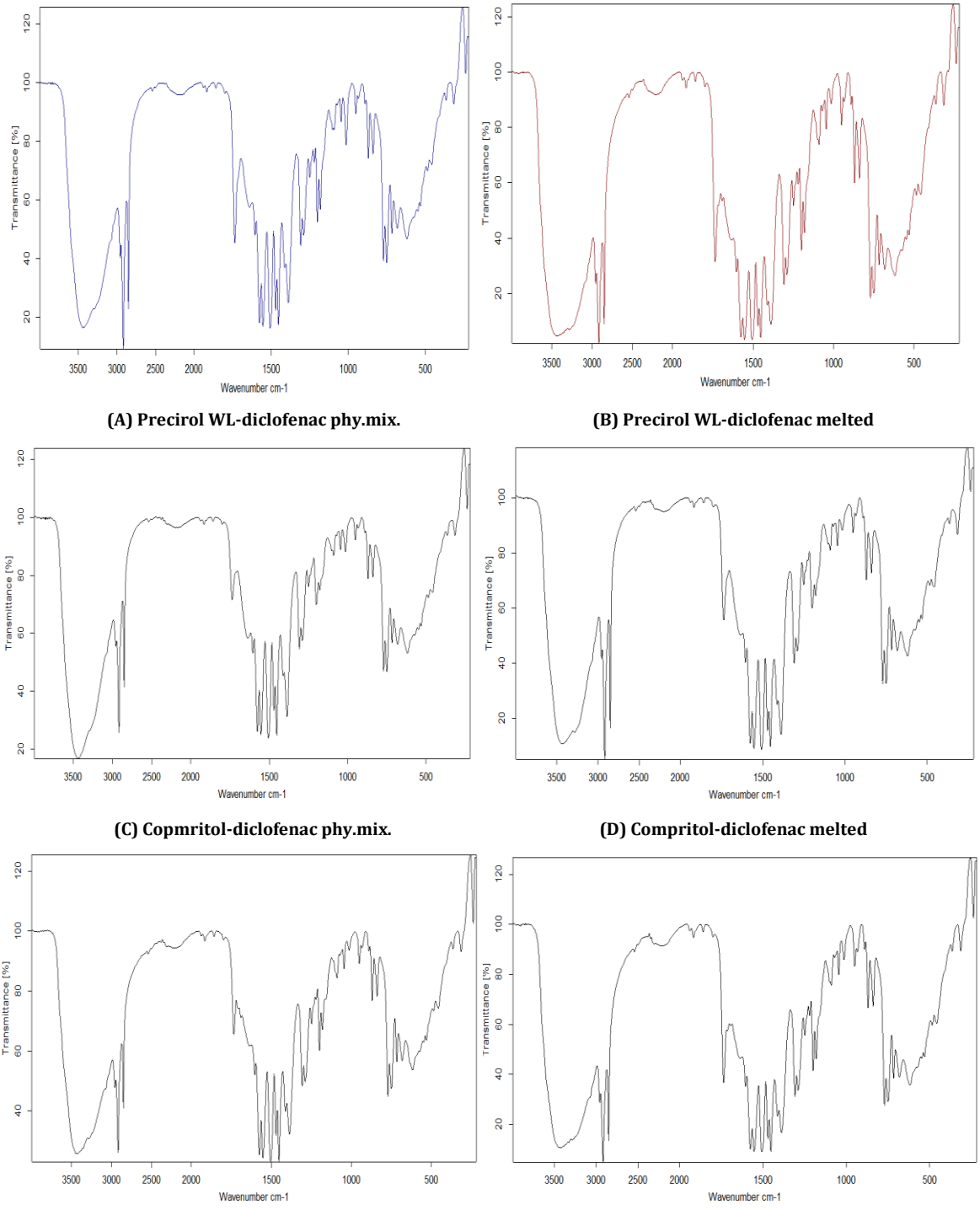
Accordingly, it was tried to indicate the effect of the value of the rapid initial drug release on the release profile from each matrix. The rapid initial drug release is the amount of drug release once the dosage form added in the dissolution media. In this study the first sample was taken and measured after half an hour. The amount of drug released after half an hour was subtracted from the cumulative drug release for each matrices. Figure 2 shows the results. From the figure it can be noticed that, the rate and amount of drug release can be arranged in the following order, precirol ATO5 melted < precirol WL melted < compritol melted < Precirol ATO5 physical mixture < precirol WL physical mixture < compritol physical mixture. Also from the same figure, it can be noticed the effect of the method of preparation of the mixture. In all cases the rate and extend of drug release from matrices prepared by melting is lower than that from matrices prepared by physical mixture.

It was reported that, during the heat treatment there are possibilities of interaction between wax and drug which could have an impact on the retardation of drug release [25].

Accordingly, as a trial to understand these changes in the drug release rate and extend, some analysis for all matrices were done.

FTIR spectroscopy is a sensitive technique to intramolecular bond structures, which affected by the arrangement of the chemical structure in a crystalline network. FTIR spectroscopy can be used to detect different polymorphs of lipids [26].

FTIR spectroscopy for all mixtures was carried out figure 3, A-F. Comparison of each spectrum of physical mixture and that prepared by heating showed that, there is no difference in the position of bands. The spectra can be simply regarded as the superposition of those of diclofenac sodium and the glycerides. This observation ruled out the possibility of chemical interaction and complex formation between diclofenac sodium and glycerides used and prepared by either as physical mixture or by melting [25, 26, 27, and 28].



(A) Precirol WL-diclofenac phy.mix. **(B) Precirol WL-diclofenac melted**

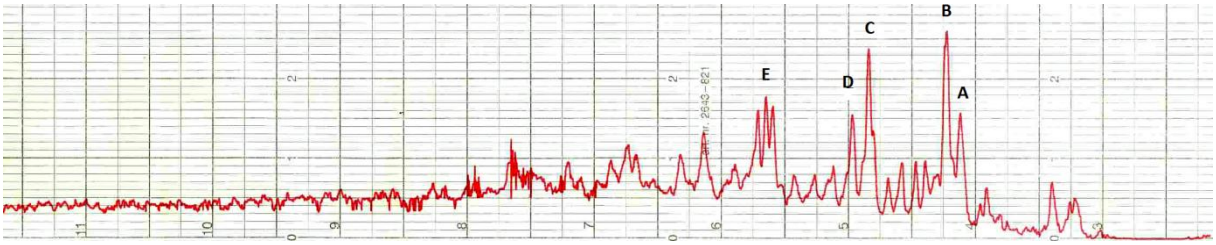
(C) Copmritol-diclofenac phy.mix. **(D) Compritol-diclofenac melted**

(E)Precirol ATO-dicolfenac phy.mix. **(F) Precirol-diclofenac melted**

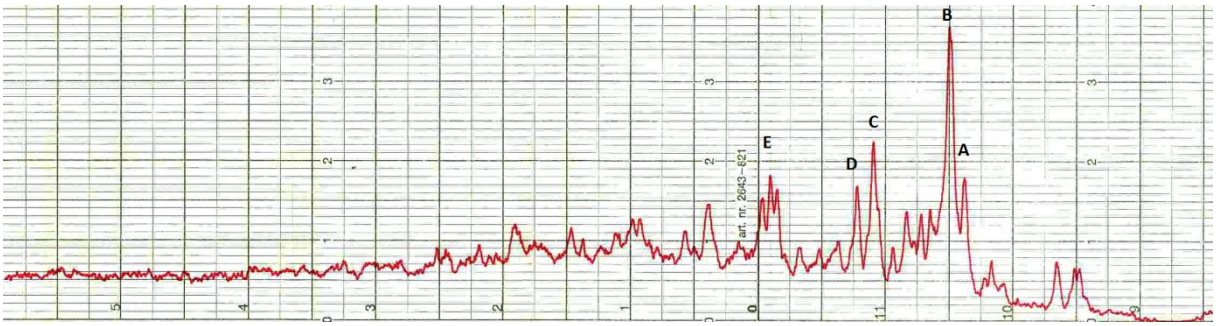
Fig. 3: Infra- Scanning for different matrices in (KRr disk).

It was reported that, the x-ray diffraction pattern of a pure substance is like a fingerprint of the substance. The powder x-ray diffraction method is thus ideally suited for characterized and identification of polycrystalline phases [29]. It was also reported that, x-ray diffraction is a much more suitable technique for the identification of the polymorphs because of their distinctive diffraction pattern [30].

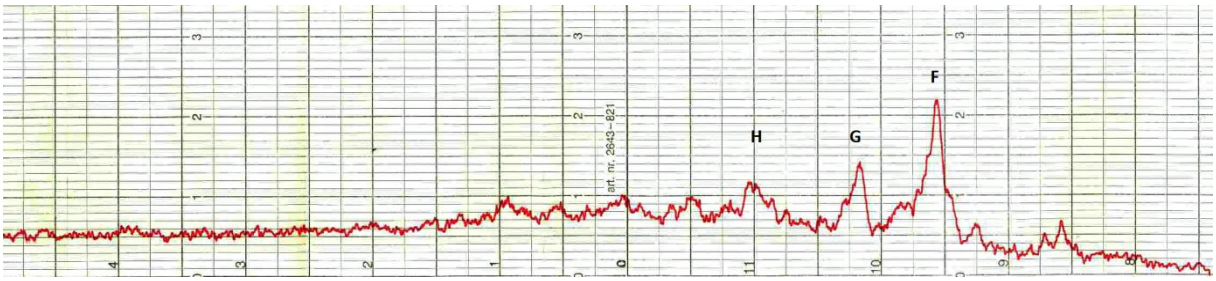
To study the effect of different glycerides on the crystallinety of the diclofenace sodium in either physical mixtures or that prepared by melteing, x-ray diffraction patterns was carried out on each mixture Figure 4, A-G. The x-ray diffraction pattern of the pure drug exhibits its characteristic diffraction peaks at various diffraction angles (A, B, C, D, E selected for comparison) indicating the presence of the drug in crystalline structure form.



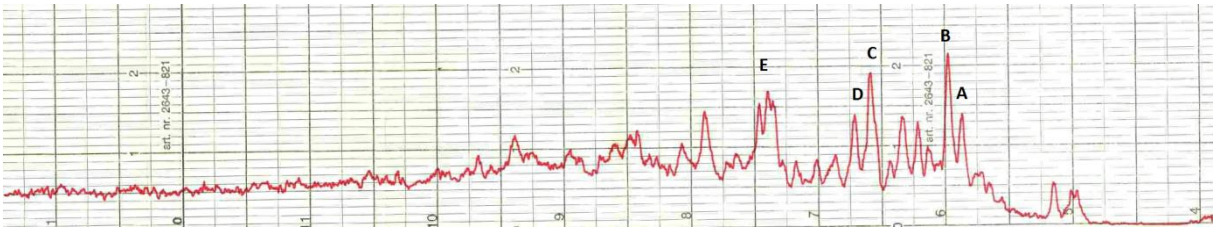
(A) Diclofenac sodium



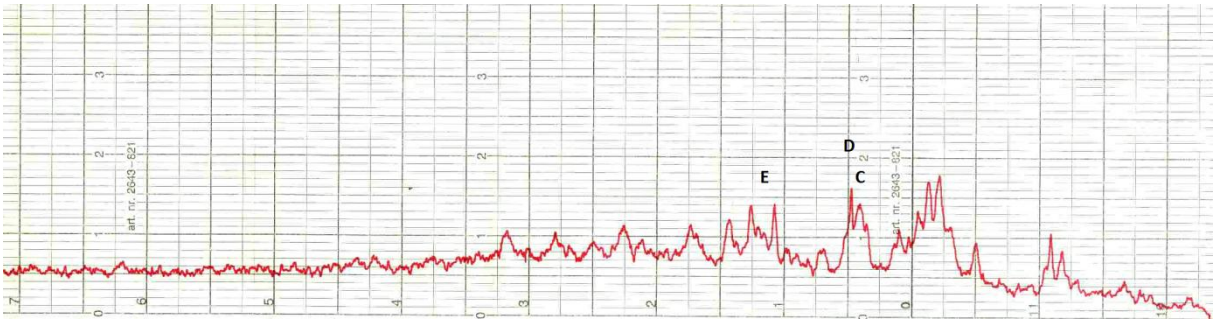
(B) Compritol-diclofenac physical mixture



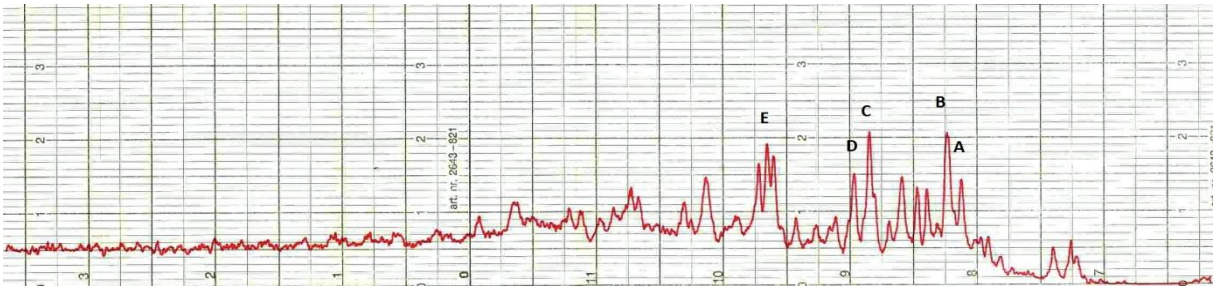
(C) Compritol –diclofenac melted



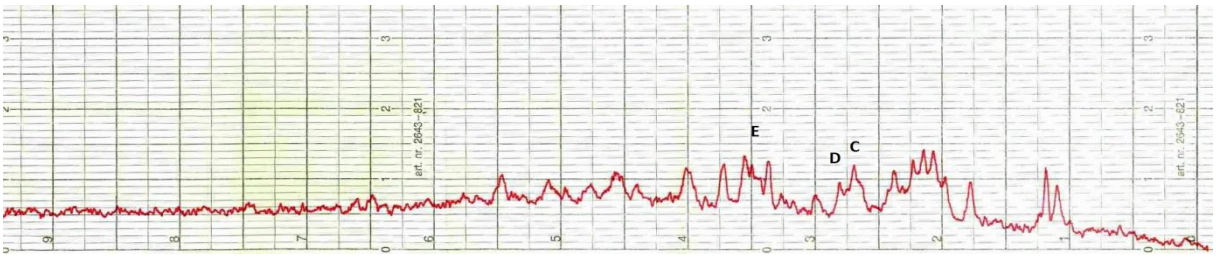
(D) Precirol WL-diclofenac physial mixture



(E) Precirol WL-diclofenac melted



(F) Precirol ATO 5-diclofenac physical mixture



(G) Precirol ATO5-diclofenac melted

Fig. 4: X-ray diffraction pattern of pure drug and the other mixtures

The characteristic diffraction peaks of diclofenac were also found in all physical mixtures of drug with glycerides. It can be also noticed that, the intensity of peak (B) in the physical mixture of comptritol with drug is higher than that in x-ray diffraction pattern of the drug alone. That is may be due to the lipidic polymorphism of compritol [21, 25]. The intensity of the peak (B) will be normal in case of physical mixture of drug with either Precirol WL or ATO 5. The characteristic diffraction peaks of the drug with compritol and prepared by melting the waxy base shows there is no evidence of drug crystal peaks. There are only broad peaks (F, G, H) shifted from the position of peaks of (B, C, D, E) of either pure drug or drug in the physical mixtures indicating there is a complete change in the crystallinety of the drug and suggesting that diclofenac is in either amorphous form or molecularly dispersion . In case of other products which prepared by either precirol WL or ATO 5, there are some characteristic diffraction peaks with small intensity (C, D, E) of drug and also the intensity of some non selected peaks showed to some extent an increase. These results are also in agreement with that stated by Vyas et all [32] who prepared solid dispersion of modafinil in different PEG and found the same change in the crysatllinity of the drug. Accordingly it can be concluded that, the drug in the bases prepared by melting the waxy matrices of either precirol ATO 5 or precirol WL are in two forms, one crystalline form and the other in non crystalline one.

Kinetics of drug release

Different semi-imperical kinetic equations were applied to interpret the release rate from different matrix system. The model that best fitting the release data was evaluated by correlation coefficient (r^2). The correlation coefficient is a measure of the strength of the straight-line or linear relationship between two variables. The correlation coefficient takes on values ranging between +1 and -1. As an accepted guidelines for interpreting the correlation coefficient value, when it is 1 indicates a perfect linear relationship and when its value between 0.7 and 1.0 (-0.7 and -1.0) indicate a strong positive (negative) linear relationship via a firm linear rule. The correlation coefficient values for all mixtures in various models are given in table 3. From the table it can be noticed that, there is a strong relationship between the data except that form both precirol WL-diclophenac physical mixture and compritol-diclofenac physical mixture. That is may be due to the using of all release data which is in agree with what stated before about two phase release pattern. The best explain for the release pattern is Higuchi model and peppas equation where the value of r^2 is between 0.98 and 0.94 indicating the diffusion mechanism of drug release.

Table 3: Regression coefficient of different kinetics models for diclofenac matrices tablets

	Zero order	First order	Higuchi kinetics	Hixson Crowell	Peppas equation
	r^2	r^2	r^2	r^2	r^2
Precirol ATO-diclofenac melted	0.937	0.940	0.984	0.939	0.943
Precirol WL-diclofenac melted	0.943	0.946	0.978	0.945	0.982
Compritol-diclofenac melt	0.862	0.871	0.946	0.868	0.974
Precirol ATO-diclofenac phs.mix	0.940	0.946	0.982	0.944	0.978
precirol WL-diclofenac phy.mix	0.522	0.549	0.654	0.540	0.764
Copmritol -diclofenac phy.mix	0.427	0.445	0.578	0.439	0.701

Table 4: Release characteristic of different diclofenac matrices tablets

	Zero order	First order	Higuchi kinetics	Hixson Crowell	Peppas	Equation
	$K_o(h^{-1})$	$K_1(h^{-1})$	$K_H(h^{-1/2})$	$K_{HC}(h^{-1/3})$	$K_{kp}(h)^{-n}$	*n value*
Precirol ATO-diclofenac melted	0.560	0.002	0.268	0.008	1.122	0.704
Precirol WL-diclofenac melted	0.854	0.003	0.406	0.013	0.485	0.530
Compritol-diclofenac melt	1.050	0.005	0.514	0.017	0.484	0.277
Precirol ATO-diclofenac phs.mix	1.722	0.008	0.822	0.028	0.653	0.701
precirol WL-diclofenac phy.mix	2.138	0.014	1.118	0.044	1.095	0.224
Copmritol -diclofenac phy.mix	2.331	0.015	1.267	0.048	0.953	0.285

The release rate constant from different mathematic models, Table 4, except peppas can be arranged in agree with what stated before as the following preceirol ATO melted < precirol WL melted < compritol melted < precirol ATO physical mixture < precirol WL physical mixture < compritol physical mixture. The values of n for different formulation have been calculated to identify the drug release mechanism, table 4. From the table it can be noticed that, the value of n is 0.277 indicating the Fickian (Case I) drug release from compritol-diclofenac melted waxy base [31]. This result is in agreement with the finding (from x-ray diffraction analysis) that the drug is either amorphous form or molecularly dispersion in the matrix. Accordingly it can be concluded that diffusion is the drug release mechanism in this case. The role of surface activity of compritol on the drug release should not be neglected [22]. Also the value of n for precirol (ATO 5 and WL) melted and precirol ATO 5 physical mixture indicating that the drug release is non-Fickian (anomalous) release. Non-Fickian refers to the summation of both diffusion and dissolution controlled drug release. This finding of mechanism of drug release is also in agreement with the result of x-ray diffraction analysis of the bases (the drug in the matrix is present in two forms, one crystalline form and the other in non crystalline one).

As a trying to elucidate the reason for two phase drug release from physical mixture of drug and either precirol WL or compritol, the correlation coefficient value and the value of n were also used. From table 5, it can be noticed that, the value of r^2 indicating there are an excellent correlation during the first 90 min dissolution process for all models. The value of n during this phase is phase indicating the non-Fickian (Anomalous) release and the release is the summation of both diffusion and dissolution. This conclusion is also supported with the finding that the release of the drug is also obeyed all other release models. Again, this finding of mechanism of drug release is also in agreement with the result of x-ray diffraction analysis of the bases (in two forms, one crystalline form and the other in non crystalline one).

Table 5: Regression coefficient of different kinetics models and release characteristic of different diclofenac from either compritol or precirol physical mixture tablets

		Compritol-diclofenac phys.mix.		Precirol WL-diclofenac phys.mix.	
		during first 90 min	*during last 360 min*	*during first 90 min*	*during last 360 min*
Zero order	**r^2**	0.999	0.671	0.977	0.883
	$K_o(h^{-1})$	23,03	0.441	19.22	0.522
First order	**r^2**	0.997	0.774	0.965	0.917
	$K_1(h^{-1})$	0.141	0.003	0.123	0.004
Higuchi kinetics	**r^2**	0.999	0.746	0.949	0.934
	$K_H(h^{-1/2})$	5.754	0.248	4.71	0.38
Hixson Crowell	**r^2**	0.995	0.773	0.969	0.916
	$K_{HC}(h)^{-1/3}$	0.448	0.009	0.386	0.014
peppas equation	**r^2**	0.996	0.711	0.954	0.946
	$K_{kp}(h)^{-n}$	0.088	1.773	0.533	1.457
	n value	0.78	0.046	0.545	0.075

From table 5, it can be also notice that, in the last 360 min of drug release from compritol physical mixture, the value of r^2 is to near to 0.7 and the rates constants is also extreme lower than the first dissolution phase. The value of n indicates the drug release occurred only by diffusion mechanism which may be due the nature of the base as waxy base. In case of precirol WL physical mixture, the value of r^2 is over than 0.9 indicating the drug release rate depend on the remaining drug in the matrix (First order model) with change in the tablet surface (Hixson Crowell model) and occurred only by diffusion (Higuchi model) with 0.075 n value. That is may be due to the nature of precirol WL as a waxy substance and its HLP value. This finding may be also in agreement with the result of x-ray diffraction analysis of the bases which indicates the crystallinity of the drug in the matrix.

CONCLUSIONS

Glecerides are still one of the most valuable matrices for control drug release. They produce high qualified granules which can be so easy formed as tablets without any complications at low concentrations. Glycerides had no chemical interaction with the drug used but there is a big difference in the existence of the drug in physical mixture form and that prepared by melting granulation technique due to change in the drug crystallinity in the matrix. This change in the crysatallininty can be detected by using x-ray diffraction technique which will reflect also on the drug release. The retarding effect depend also the type of glecerides and the nature of the drug used as well as the method of preparation.

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