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FORMULATION AND EVALUATION OF DEXIBUPROFEN MATRIX TABLETS FOR ORAL CONTROLLED DRUG DELIVERY

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ABSTRACT

Dexibuprofen[S (+)-Ibuprofen] is used in the symptomatic treatment for osteoarthritis, muscular pain and inflammation. The purpose of the present research work was to develop controlled release matrix tablets of dexibuprofen by direct compression technique using different concentrations of hydroxyl propyl methyl cellulose (HPMC-K15M) Kollidon SR (Polyvinyl acetate & povidone) as polymers and Pharmatose 200M as diluent. The drug excipients mixtures were subjected to preformulation by FTIR, DSC and XRPD studies. The different in-process and finished product quality controlled tests of the formulations were evaluated and found within the pharmacopeias limits *In-vitro* drug release was estimated in simulated gastric fluid (SGF) pH1.2 for initial 2h, shows ≤ 20% w/w and simulated intestinal fluid (SIF) pH 7.4 > 60 %w/w followed by sustaining up to 12 h. The swelling behaviors of formulated tablets remarkably increase with optimum proportion of polymer and diluent level. Based on the in-vitro dissolution data the optimized formulations DX-4 and DX-9 were best fitted to huguchi matrix followed by Korsmeyer and Peppa's model, shows diffusion co-efficient values in between n=0.8306 and 1.1356, indicates the drug release from matrix tablets by both diffusion and erosion mechanisms controlled by diffusion of swellable thick polymeric gel layer matrices.

KEYWORDS: Dexibuprofen, Oral controlled release, Matrix tablets, Kollidon SR, Higuchi matrix kinetics, Zero-order kinetics.

INTRODUCTION

A wide variety of newer drug delivery systems such as sustained/controlled release oral products are being fabricated and investigated in recent years to improve bioavailability of conventional drug delivery required to patients for long therapy in acute diseases conditions. They offer once-daily or twice daily dosing and are able to achieve optimum therapeutic drug concentration in the blood with minimum fluctuation, reduce frequency of adverse effects improving therapy, safety, efficacy and patient compliance.[1]

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly prescribed categories of drugs worldwide owing in their efficacy as anti-inflammatory, anti-thrombotic, anti-pyretic and in the treatment of pain and inflammation in many conditions.[2] During the past 30 years, there has been a substantial increase in the number of clinically available NSAIDs. They annually account for 70 million prescriptions and 30 billion over-the-counter (OTC) medications sold in the worldwide. Population studies have shown that 10–20% of peoples who are 65 years or older are currently receiving a prescription for NSADs drugs it may be expected to increase from 380 million to 600 million.[3]

Dexibuprofen[S (+)-Ibuprofen] is a novel NSAID considered as pharmacologically active enantiomer of racemic Ibuprofen with analgesic action which acts by inhibiting prostaglandin synthesis, used for the management of pain and inflammation associated with osteoarthritis including dysmenorrhea, dental pain with dose range 200-400mg 2-3 divided doses as conventional tablets.[4] Adverse gastrointestinal disorders have been observed due to its short biological half-life 1.8-3.5h requires multiple dosing. It leads to fluctuations in the drug blood levels and dose related adverse effects, multiple dosing also fail to release the drug at the desired rate and in the desired amount which often results in poor patient compliance and inefficient therapy.[5] The great therapeutic value of dexibuprofen has made necessary to develop oral controlled release products namely matrix tablets by control onset of action in various physiologic environment using certain water swellable and non-swellable polymeric materials to avoiding the gastrointestinal risks.

The matrix tablets are one of the least complicated approaches to the manufacture of oral sustained release dosage forms including active drug, retardants and other excipients by direct compression or wet-granulation techniques. The release of the drug from the tablets by dissolution controlled as well as diffusion/erosion controlled mechanisms.[6] The drug release

is controlled by adding the active drug into swellable hydrophilic or insoluble non-swellable matrix materials.

The hydroxyl propyl methyl cellulose (HPMCK15M) is hydrophilic swellable polymer used as coating agent, stabilizing agent, tablet binder, viscosity modifier and suspending agent in various pharmaceutical products.[7] HPMC is an swellable hydrophilic polymer have been widely used as drug release modifier in several sustained / controlled drug delivery systems due its most advantageous properties such as biocompatibility, biodegradability, ability to modify the properties of aqueous environment, capacity to thicken, emulsify, stabilize, encapsulate, swell and to form gels.[8] Kollidon SR is polyvinyl acetate and povidone based matrix retarding agent. Polyvinyl acetate is a very plastic material that produces a coherent matrix even under low compression forces. When the tablets are introduced into gastric or intestinal fluid, the water soluble povidone is leached out to form pores through which the active ingredient slowly diffuses out wards. Kollidon SR can be used for the production matrix tablets, pellets and granules by using direct compression, roller compaction, wet granulation and extrusion. The excellent flowability and compressibility of Kollidon SR is suitable for the manufacture of sustained release tablets obtained by direct compression.[9] The aim of the present study, which was to develop matrix tablets of dexibuprofen were prepared by direct compression techniques by using hydroxyl propyl methylcellulose (HPMCK15M), Kollidon SR as release retardants, Pharmatose 200M as diluent and Primojel as a disintegrant. The effects of polymer and diluent ratio on the certain preliminary characterizations of tablets such as hardness, average weight, percentage of weight variation, percentage friability, and percentage of drug content, swelling ratio and in-vitro drug release potential were evaluated according to pharmacopeias methods.

MATERIAL AND METHODS

Materials

Dexibuprofen was obtained as a gift sample from Emcure Pharm Ltd., Pune, India. HPMC-Methocel K15M was gift sample from Colorcon Asia Private Ltd. Goa. Kollidon SR; Polyvinyl acetate & povidone were gift sample from signet chemicals Pvt, Ltd. Mumbai. Pharmatose200M (Lactose monohydrate), Prejel PAS PH; Primojel Type A were gift samples from DMV-Fonterra, Netherland. Magnesium stearate and Purified talc were purchased from Loba chemicals Mumbai. All other reagents and solvents used were of analytical grade satisfying pharmacopoeias specifications.

PREFORMULATION STUDIES

FT-IR Spectroscopic Analysis

Drug polymer interactions were studied by FT-IR spectroscopy. Two milligrams of dexibuprofen alone, mixture of drug and polymer were weighed and mixed properly with potassium bromide uniformly. A small quantity of the powder was compressed into a thin semitransparent pellet by applying pressure. The IR- spectrum of the pellet from 450-4000cm^{-1} was recorded taking air as the reference and compared to study any interference.

Differential Scanning Calorimetry (DSC)

Differential scanning calorimetry (DSC) was performed using DSC-60 (Shimadzu, Tokyo, Japan) calorimeter to study the thermal behaviors of drug alone and mixture of drug and polymer. The instrument comprised of calorimeter (DSC-60), flow controller (FCL-60), thermal analyzer (TA-60) and operating software (TA-60). The samples were heated in sealed aluminum pans under nitrogen flow (80ml/min) at a scanning rate of 10 degree centigrade/m from 25 to 450 degree centigrade. Empty aluminum pan was used as reference. The heat flow as a function of temperature was measured for the drug and drug -polymer mixture.

X-Ray Powder Diffractometry (XPRD)

The X-ray diffraction patterns of pure drug and the drug loaded formulations were recorded using Philips X-ray powder Diffractometry (Model; PW 1710) with copper target to investigate the crystallinity of drug. Powder X-RD patterns were recorded using a radiation at 30kv and 25mA, scanning speed 20/m^{-1}, over the 4^0 to 40^0 diffraction angle (2θ) range.

Preparation of dexibuprofen matrix tablets

Ten batches of dexibuprofen tablets were prepared corresponding to various drugs to polymer ratio by direct compression technique. All ingredients were accurately weighed and mixed in a polybag. These powders were passed through sieve No. 60 ASTM (American Society of Testing and Materials) and then mixed in a large size poly bag using tumbling action. Finally magnesium stearate and talc were mixed properly and compressed into 600 mg weight of tablets using a single-punch compression machine (Cadmach Ahmedabad, India) at 6-7 kg/cm^2 of hardness. **Table 1** summarizes the batch details of dexibuprofen matrix tablets.

Table.1. Batch details for the formulation of dexibuprofen matrix tablets

Ingredients	Batch Code									
	DX-1	DX-2	DX-3	DX-4	DX-5	DX-6	DX-7	DX-8	DX-9	DX-10
Dexibuprofen	300	300	300	300	300	300	300	300	300	300
HPMC K15M	25	50	100	150	200	-	-	-	-	
Kollidon SR	-	-	-	-	-	25	50	100	150	200
Pharmatose 200M	225	200	150	100	50	225	200	150	100	50
Prejel PAS PH	20	20	20	20	20	20	20	20	20	20
Primojel	10	10	10	10	10	10	10	10	10	10
Mag. stearate	15	15	15	15	15	15	15	15	15	15
Purified talc	5	5	5	5	5	5	5	5	5	5
Theoretical weight of each tablets = 600 mg										

PHYSICOCHEMICAL EVALUTION OF MATRIX TABLETS

Micromeritic properties of precompressed powder

The flow characteristics of the different batches pre-compressed powder were measured by determining their angle of repose using fixed-base cone method. A glass funnel was secured with its tip positioned at a fixed height (H) above graph paper placed on a horizontal surface. The sample was poured through the funnel until the apex of the conical pile touched to the tip of the funnel. The height and radius of the heap was measured.[10] The experiment was repeated in triplicate, the angle of repose (tan θ) was calculated using the formula;

$$\text{Angle of repose}[\theta] = \tan^{-1}(h/r)$$

H = cone height, r = radius of circular base formed by the granules on the ground.

The bulk and tapped densities of the pre-compressed powder were evaluated by using the bulk density apparatus. Known weights of formulated granules were transferred into a 50cc graduated measuring cylinder. The cylinder was fixed on bulk density apparatus and the timer knob was set for 100 tapings. Then, the initial bulk volume and final volume after 50 tapings were noted. The experiment was repeated in triplicate.[11] The respective densities of different batches of granules were calculated by using the following formulas;

$$\text{Bulk density [gm /cc]} = \frac{\text{Mass of the sample (g)}}{\text{Bulk volume (ml)}}$$

$$\text{Tapped density [gm/cc]} = \frac{\text{Mass of the sample}}{\text{True volume}}$$

Compressibility index or Carr's index value of precompressed was computed according to the following equation;

$$\text{Carr's index (CI \%)} = \frac{\text{Tapped density - Bulk density}}{\text{Tapped density}} \times 100$$

Hausner's ratio of precompressed powder was determined by comparing the tapped density to the bulk density by using the equation;

Hausner's ratio = Tapped density / Bulk density

Weight variation, Hardness and Friability

The uniformity of weights of tablets was determined according to the method mentioned in Indian pharmacopeia.[11] Weighed 10 tablets individually in an electronic balance and their average weight were determined. The standard deviation was calculated using the following formula;

Average weight (gm) = Total weight of the tablets /10

Standard deviation (%) = (Iw – Aw / Aw) x 100

[Where, Iw = Individual weight of the tablets, Aw = Average weight of the tablets]

For each formulation, the hardness of 10 randomly selected matrix tablets was examined using a Pfizer hardness tester (A-101 Secor India). The tablet hardness or crushing strength was measured in kg/cm2.

The percentage of friability was evaluated by using Roche friabilator (USP EF-2 Electro Lab). Ten or twenty tablets from each batch were weighed and placed in the plastic chamber. The chamber rotated for 4 minutes or 100 revolutions. After 100 revolutions tablets were removed from the chamber and reweighed.[12] The percentage of weight loss or friability was determined by the following formula;

Friability (%) = Loss in weight of tablets / Initial weight x 100

Swelling behavior of tablets

The swelling ratio of three matrix tablets from each formulation was determined. The weighed tablets were placed in a glass beaker containing 500 ml of phosphate buffer at pH 6.8 ± 0.1 at 37 °C with continuous stirring at 50 rpm. After 0.5, 2, 4 and 6 h time period intervals the tablet was removed and blotted with tissue paper. The tablet was weighed on a digital balance (GE-412 Sartorius) and the final weight of the tablet was noted after

prescribed time. The experiment was performed in triplicate for each time point and fresh samples were used for each individual time point.[13] The extent of swelling was measured in terms of percentage weight gain by the tablet was calculated by the following formula;

Swelling index (S.I) = [(Mt-Mo) / Mo] X 100

[Where, Mt = weight of tablet at time =t and Mo = weight of tablet at time t=0]

Drug content uniformity

Five tablets of each batch were weighed and powdered. The quantity of the powder equivalent to 300 mg of dexibuprofen was suspended in 100 ml of phosphate buffer pH 6.8 ± 0.1 containing 10 ml of methanol. The resulting solution was transferred into a stoppered conical flask and the flask was shaken for a period of 12 h by using a mechanical shaker at room temperature. Next day it was stirred for 15 minutes. The solution was filtered, after suitable dilution; the drug content in the filtrate was analyzed at λ max 264.5 nm using UV-Visible spectrophotometer (Shimadzu 1201).[14] The obtained absorbance was plotted on the standard curve to get the exact concentration of the entrapped drug. Each experiment was carried out in triplicate (n=3). The actual drug content was determined by using the following relationship;

$$\text{Drug content} = \frac{(k \times \text{Absorbance} \pm B) \times \text{bath volume} \times \text{dilution factor}}{1000}$$

***In-vitro* drug release studies**

The various batches of the compressed matrix tablets of dexibuprofen was subjected to estimation of drug release in the simulated gastric fluid (SGF) of pH 1.2 from 0 - 2 h and simulated intestinal fluid (SIF) pH of 7.4 up to 12 h by using dissolution test apparatus USP XIII paddle type (Model-TDT-08L, Electrolab Mumbai, India). The drug loaded matrix tablets were put into the basket rotated at a constant speed 75 rpm in 900 ml dissolution medium of pH 1.2 SGF was used for initial 2h and continued the test by changing the dissolution media pH 7.4 SIF up to the end of 12h and maintained temperature 37 ± 2^0C. Samples (5ml) were collected at 0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 10 and 12h time period. After each sampling, equal volume of the medium was replaced with same volume of fresh medium. The sample was filtered through 0.45µ membrane filter and diluted with appropriate dilution with respective medium. Then estimate the dexibuprofen concentration in the solution by using UV-Visible spectrophotometry (Shimadzu 1201, Japan) measured at λ max 264.5 nm.[15, 16] The absorbance of the samples was measured at different time intervals and

the concentration, amount of drug released and the percentage of drug release were calculated using the following formulas;

Concentration (µg/ml) = Slope X Absorbance ± Intercept

$$\text{Drug released} = \frac{C \times VD \times DF}{1000} \times 100$$

Where; C= Concentration (µg/ml), VD= volume of dissolution media, DF= dilution factor.

$$\text{Percentage drug release (\%)} = \frac{\text{Amount released}}{\text{Drug content}} \times 100$$

Mechanism of drug release kinetics studies

The data obtained from the in-vitro dissolution studies was subjected to kinetic treatment to obtain the order of release and best fit model for the formulations by using PCP-Disso-V2 software. The in-vitro drug release drug release data of the formulations was analyzed with various kinetic equations like zero-order (% release v/s time), first- order (Log % retained v/s time), Higuchi matrix (cumulative % drug released vs. square root of time) and Korsemeyer and Peppas equation (Log cumulative percent drug released versus log time).[17] The coefficients of correlation (r) values were calculated for the linear curves obtained by regression analysis of the above plots.

Zero-order kinetics: The drug release followed by zero-order was estimated by using the following equation;

$Q_t = Q_0 + K_0 t$

Where Q is the amount of drug dissolved in time t, Q_0 is the initial amount of drug in the solution (most times Q =0), and K_0 is the zero order release constant. When the data is plotted as cumulative percent drug release versus time, if the plot is linear then the data obeys zero-order release kinetics with a slope equal to K_o.

First-order kinetics: The drug release followed to first-order was estimated by using the following equation;

$\text{Log } c = \text{Log } Co - K_t / 2.303$

Where: C = Amount of drug remained at time (t). Co = Initial amount of drug, K=First-order rate constant (hr^{-1})

When the calculated data was plotted as log cumulative percent drug remaining versus time obtained a straight line that indicates that the release follows first order kinetics. The constant 'K' can be obtained by multiplying 2.303 with slop values.

Higuchi's matrix model: This model explains the release of drug from matrix devices mainly by diffusion of drug from the matrix layer. The drug release from the formulations was determined by using the following Higuchi's classical diffusion equation.

$Q = [DE / \tau (2A - E Cs) C_{st}]^{½}$

Where; Q = Amount of drug released at time (t), D = Diffusion co-efficient of the drug in the matrix, A = Total amount of drug in unit volume of matrix, Cs = the solubility of the drug in the matrix, E = Porosity of the matrix, τ = Tortuosity and t = time (hrs.) of which Q amount of drug is released.

The above equation can be simplified if one assumes that D, Cs and A are constant. The equation becomes

$Q = Kt^{½}$

When the data was plotted by cumulative percentage of drug release versus square root of time shows a straight line. This was indicates that the drug was released by diffusion mechanism.

Korsemeyer and Peppas model: This model was generally used to analyze the release of the drug from polymeric dosage forms, when the release mechanism is not well known or when more than one type of release occurs corresponding to time (t). In order to understand the mode of drug release from swellable matrices, the data is fitted to the following Peppas equation

$M_t / M_\infty = K t^n$

Where, Mt is the amount of drug released at time (t). M∞ is the amount of drug released at infinite time (t). K is the kinetic rate constant depends on structural and a geometric characteristic of the product and n is the diffusional exponent which indicates the release mechanism.[18] The above equation can be simplified by applying log on both sides then we get:

$\text{Log } Mt / M\infty = \text{Log } K + n \text{ Log } t$

When the data is plotted as log percentage of drug release versus log time shows a straight line with a slope equal to 'n' (diffusional co-efficient) and the 'K' (coefficient of correlation) can be obtained from y-intercept.

RESULTS AND DISCUSSION

Preformulation studies

The preformulation is the preliminary study for investigation and detail understanding of the physicochemical and chemical dynamics of drug substances through stability under the conditions to select correct form of drug and non-drug components for developing optimal drug delivery system.[19] Based on the preformulation results, proper excipients are used in the manufacturing of protocol products and to optimize the release of drug for an extended period at the site of action.

FT-IR spectroscopy

The FTIR spectra's, observed that the characteristic absorption peaks of pure dexibuprofen were obtained at 3087.56, 2994.16, 1707.56, 1460.7, 13620.10 and 705.5cm-1 corresponding to O-H, C-H, C=O C-C, C-O stretching and OH- bending **(Figure1a)**. FTIR spectra of HPMC K15M show the characteristic peaks at wave numbers 2815.33, 1706.56, 1485.32, 1385.36 and 782.60 cm-1 corresponding to C-H stretching, C=C stretching in the aromatic ring and peaks at 1485.32, 1385.36 cm-1 which can be assigned to the C-H deformation **(Figure 1b)**. The FT-IR spectra of the physical mixture of dexibuprofen and HPMC K15M shows the characteristic peaks at wave number 3185.50, 2985.35, 1735.25, 1495.65, 1405.25 and 715.36 cm-1 corresponding to O-H, C-H, C=O C-C, C-O stretching and OH- bending **(Figure 1c)**. The characteristic absorption peaks of Kollidon SR were observed in the region of 3315.42, 2996.52, 1745.55, 1695.30 1480.50, 1375.66 and 694.25 cm-1 and represents O-H, C-H, C=O stretching vibration. The peaks observed at 1375.66 corresponding to CH2 wagging and 694.25 cm-1 represents skeletal C–H rocking **(Figure 1d)**. The physical mixture of Kollidon SR and dexibuprofen shows characteristic absorption peaks in IR-spectra at wave numbers 3319.50, 2909.11, 1710.92, 1585.5, 1418.32 and 669.53cm-1 corresponding to O-H, C-H, C=O stretching vibration and C-H deformation **(Figure 1e)**. The IR spectra's of individual polymer and physical mixtures of drug and polymer were compared with the spectra of the pure drugs. The spectral data suggests that the major peaks for drugs are obtained as nearer value and there were no considerable changes in IR peaks in all physical mixtures of drug and polymer. This indicates that the drugs were molecularly dispersed in the polymers or in drug loaded formulations thus thereby indicating the absence of any interactions.

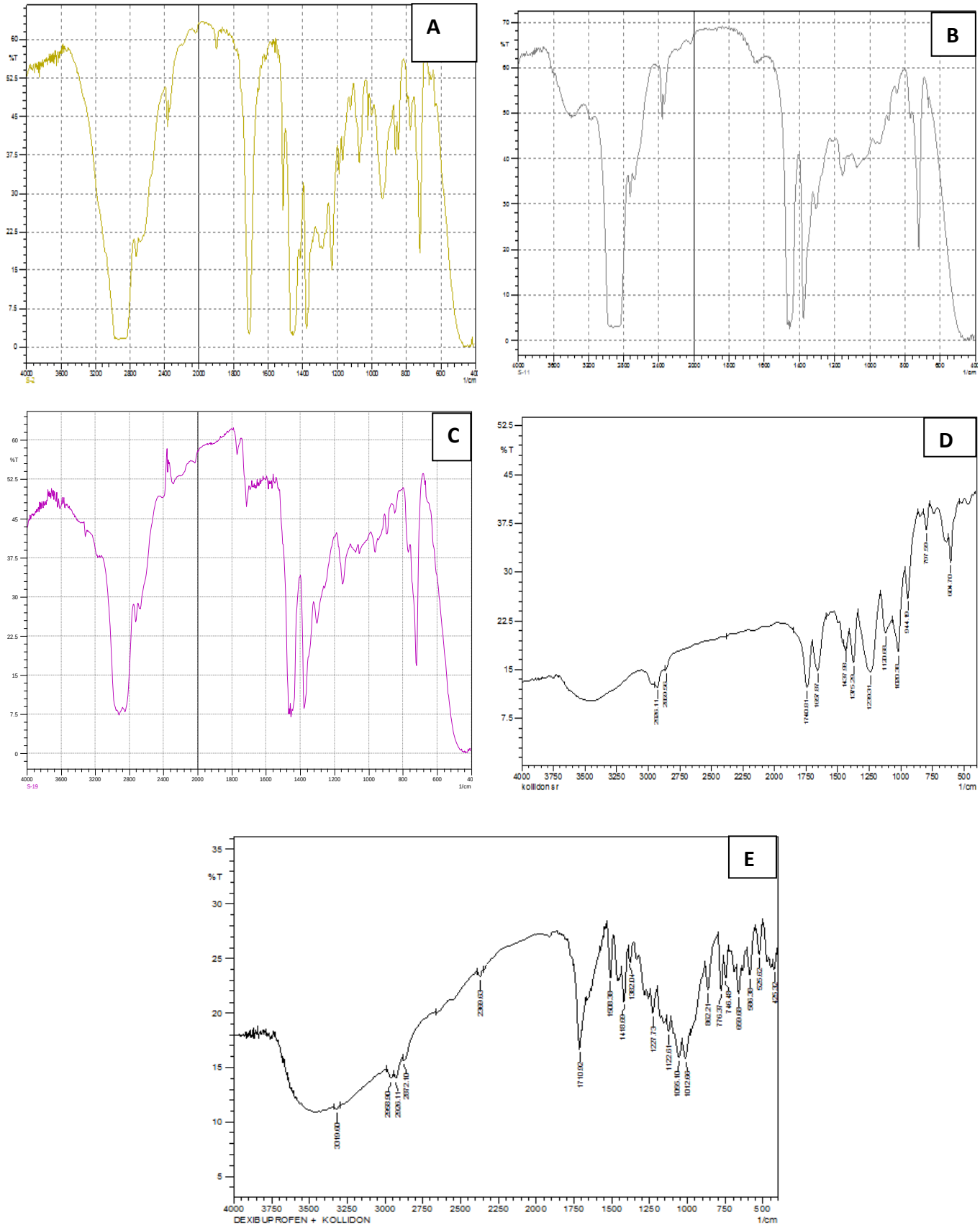


Figure 1. FTIR-Spectra of A) Pure dexibuprofen B) HPMC K15M C) Physical mixture dexibuprofen and HPMC K15M D) Kollidon SR E) Physical mixture of dexibuprofen and Kollidon SR

Differential scanning calorimetry (DSC)

DSC is a well-established method often used as a qualitative technique to characterize physical and chemical changes in either enthalpy or heat capacity of a crystalline drug in the polymer matrix during the manufacturing process. The thermogram of pure dexibuprofen showed a sharp endotherm at 55.50^{0}C followed by 400^{0}C corresponding its meting point **(Figure 2a)**. However, the drug-loaded matrix tablets showed a broad endotherm at 55.5^{0}C and a sharp endotherm at 405^{o}C **(Figure 2b and 2c).** The distinctive endothermic peak of dexibuprofen at 55.5^{0}C was absent in the formulated matrix tablets. There was no appreciable change in the melting endothermic peaks of drug loaded formulations compared to pure drug. It may indicate that there are no changes in thermal behavior of drug in the manufacturing process and the drug was molecularly dispersed in different hydrogel matrices.

X-Ray Powder Diffractometry (X-RPD)

The distribution of the drug in the polymeric matrix is very important to maintain the theoretical potency and stability in the manufacturing process. However, the drug can crystallize during the formulation resulting decreased aqueous solubility rate due to its polymorphic changes such as particle size, shape, density, melting point etc. The XRPD is an important technique in pharmaceutical field because to investigate the fundamental physical features about the crystalline nature of solid substances.

The X-ray powder diffraction patterns of pure drug were compared with drug-loaded matrix tablets. The relative intensity of peaks were observed in XRPD patterns and calculated by using D8 TOOLS software. The intensity of pure dexibuprofen peaks observed at 10.47, 12.18, 19.68 25.25 and 39.65 (2θ) **(Figure 3a).** The dexibuprofen formulated tablets DX-4 and DX-9 shows the intensity of peaks at 22.39, 26.02 (2θ) and 20.45, 25.12(2θ) respectively **(Figure 3b and 3c).** The XRPD scan of plain dexibuprofen shown sharp intense peaks of crystallinity whereas the drug-loaded matrix tablets exhibited halo pattern with less intense followed by denser peaks. This result indicates that decrease in the degree of crystallinity due to partial amorphization of the drug in the polymeric matrix. Thus, there were no appreciable changes in the crystallinity of drug during the manufacturing process.

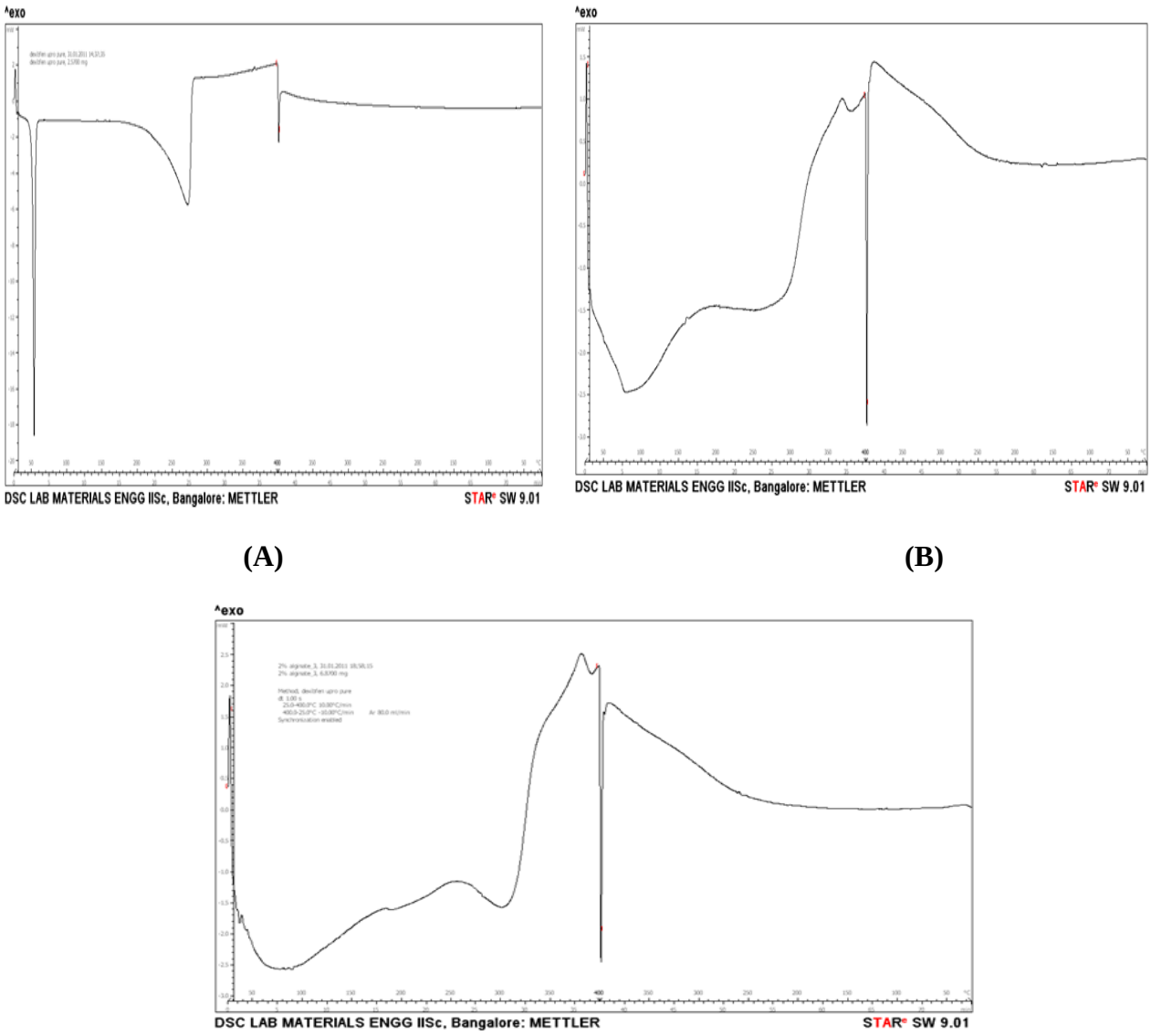
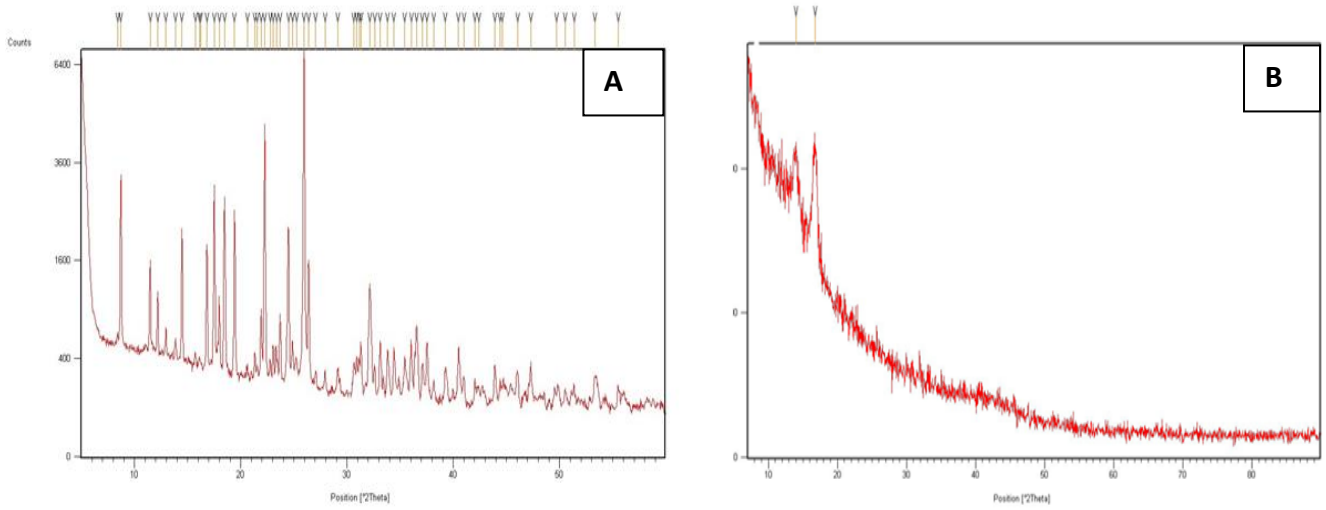


Figure 2 DSC Thermo-grams of a) pure dexibuprofen b) Dexibuprofen matrix tablets (DX-4), c) Dexibuprofen matrix tablets (DX-9)



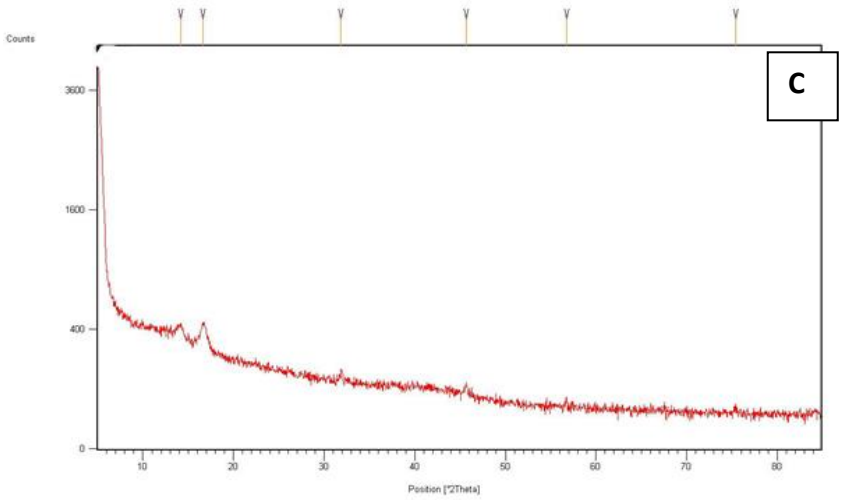


Figure 3 X-Ray diffraction patterns of A) Pure dexibuprofen B) Matrix tablets containing HPMC K15M as retardant (DX-4), C) Matrix tablets containing Kollidon SR as retardants (DX-9)

Micromeritic properties of precompressed powder blends

Direct compression method was employed in the production of many oral controlled release dosage forms to achieve prolonged release of drug from matrix-type particles. The polymer diluent ratio significantly influences the micromeritic properties of powder blends. The dexibuprofen is a crystalline substance that induces flow properties when blended with other excipients due to the formation of strongly bonding surfaces held together by the presence of crystalline of finite strength. The powder blends of different formulations (DX-1 to DX-10) were evaluated for angle of repose, loose bulk density, tapped bulk density, Carr's index, and hausner's ratio. From the Table 2; the increase in the concentration of polymer and diluent ratio decreases the angle of repose. All the formulations powder blends show angle of repose (<30) indicating good flow properties due to increase of bonding between microcrystals of drug and diluent. The bulk and tapped density values were obtained in the acceptable range indicating good packability. Compressibility index and hausner's ratio values are obtained in the range of 15.96 to 7.65 and 1.22 to 1.10 respectively. This indicates that the prepared powder blends having excellent compressibility and good flow properties get acceptable hardness to the tablets.

Table 2 Micromeritic properties of pre-compressed powder blends of dexibuprofen

Formulation Code	Bulk density (g/ml)	Tapped density(g/ml)	Carr's index (%)	Hausner's ratio	Angle of repose (θ)
DX-1	0.312 ± 0.25	0.347 ± 0.47	14.95	1.22	24.40 ± 0.92
DX-2	0.335 ± 0.35	0.386 ± 0.25	13.25	1.17	22.90 ± 0.98
DX-3	0.368 ± 0.22	0.416 ± 0.16	11.53	1.15	22.40 ± 0.58
DX-4	0.405 ± 0.12	0.454 ± 0.54	10.80	1.14	20.60 ± 0.68
DX-5	0.446 ± 0.10	0.482 ± 0.28	07.65	1.10	19.70 ± 0.37
DX-6	0.583 ± 0.23	0.702 ± 0.08	16.95	1.20	18.70 ± 0.25
DX-7	0.636 ± 0.27	0.757 ± 0.27	15.96	1.19	17.10 ± 0.50
DX-8	0.705 ± 0.18	0.823 ± 0.23	14.33	1.16	16.40 ± 0.30
DX-9	0.745 ± 0.44	0.853 ± 0.53	12.66	1.14	16.10 ± 0.87
DX-10	0.786 ± 0.15	0.886 ± 0.68	11.25	1.12	15.80 ± 0.89

Data are expressed as mean ±SD of at least triplicate

EFFECT OF POLYMER TO DILUENT RATIO ON PHYSICOCHEMICAL PROPERTIES OF MATRIX TABLETS

Effect of HPMC K15M and Pharmatose 200M

The Table 3; illustrates that the weight variation of the matrix tablets observed within pharmacopeia limit complied below ±5% w/w of standard deviation from the average. The average weight of the matrix tablet of the batch DX-4 was obtained very nearer to theoretical weight. It stated that the weight variation of formulated dexibuprofen tablets was influenced by both polymer and diluent content. The hardness of the formulated tablets with variations of polymer and diluent concentration was obtained within acceptable range of 4.8 ± 0.58 to 5.6 ± 0.16 kg/cm^2 followed by decreasing the percentage of friability except the batch DX-1. This indicates the low concentration of HPMC K 15M used in the formulation decreases the mechanical strength due formation of loose matrix network with high concentration of diluent (Pharmatose 200M). The content of dexibuprofen present in the formulated tablets was observed in the range of 77.66 ± 0.84 to 96.85 ± 0.82 %w/w. It stated that the percentage of drug content influences mainly by increasing the concentration of HPMC K15M entrapped more quantity of drug due to the formation of dense matrix during compression.

The percentage of swelling ratio increases with increasing in the concentration of both polymer and diluent. The percentage of swelling ratio was observed in the range of 188.20, 196.55, 206.30, 286.30 and 236.55 at the end of 6 hours **(Figure 4)**. The formulation DX-1 containing higher level of Pharmatose 200M (above 200mg) shows higher swelling in initial hours followed by erosion at the end of 6 h because the hydrophilic moieties of Pharmatose 200M forms more micro-cavities in polymer matrices and these induces the swelling and

erosion of matrices observed in dissolution media. The formulation of batch DX-5 containing more concentration of polymer and less concentration of diluent slightly decreases the swelling ratio but controls erosion. The optimum concentration of polymer and diluent ratio shows steady state swelling ratio at 6 h time period. This explains that the presence of higher level of HPMC K15M enhances the formation of gel inhibiting water penetration into interior layer of polymeric gel net-work and thus gradually swells with increasing time period.

The dexibuprofen release from the matrix tablets significantly increases by increasing the concentration of HPMC K15M and Pharmatose 200M ratio in the formulation. The percentage of dexibuprofen release from the tablets of batches DX-1 to DX-5 was obtained in the range of 29.63, 24.52, 20.23, 16.56, and 12.86 in SGF pH 1.2 for initial 2 h due to poor solubility of dexibuprofen in this environment. On the other hand, the percentage of drug release was observed in pH 7.4 SIF in the range of 99.36, 95.12, 87.65, 75.63 and 69.55 at the end of 12 h **(Figure 5).** The formulation batch DX-5 was more sustained compared to DX-1 because of higher concentration of HPMC K15M in the matrix tablets prolongs the drug release extended period due to formation of thick diffusion gel layer which acts as a barrier, take prolonged time to diffuse the drug into bulk of the dissolution media.

Table 3 Physicochemical evaluation of the formulated matrix tablets of aceclofenac sodium

	Evaluation parameters				
	Average weight(mg)	**S. D. (%)**	**Hardness (kg/cm2)**	**Friability (%)**	**Drug content (%)**
DX-1	598.20	0.33	4.8 ± 0.58	0.68 ± 0.09	77.66 ± 0.84
DX-2	594.10	0.55	5.0 ± 0.32	0.57 ± 0.18	84.77 ± 0.56
DX-3	602.30	0.23	5.2 ± 0.42	0.53 ± 0.22	90.58 ± 0.85
DX-4	600.40	0.06	5.6 ± 0.16	0.48 ± 0.15	95.52 ± 0.55
DX-5	584.50	1.22	5.4 ± 0.65	0.45 ± 0.13	96.82 ± 0.85
DX-6	610.10	1.14	5.2 ± 0.33	0.60 ± 0.15	87.76 ± 0.84
DX-7	608.30	1.05	5.5 ± 0.28	0.52 ± 0.18	89.52 ± 0.66
DX-8	598.10	0.55	5.8 ± 0.44	0.45 ± 0.15	94.82 ± 0.95
DX-9	600.50	0.45	5.4 ± 0.8	0.48 ± 0.25	97.62 ± 0.75
DX-10	592.20	0.68	5.0 ± 0.25	0.51 ± 0.15	98.42 ± 0.55

Data are expressed as mean ±SD of at least triplicate (n=3)

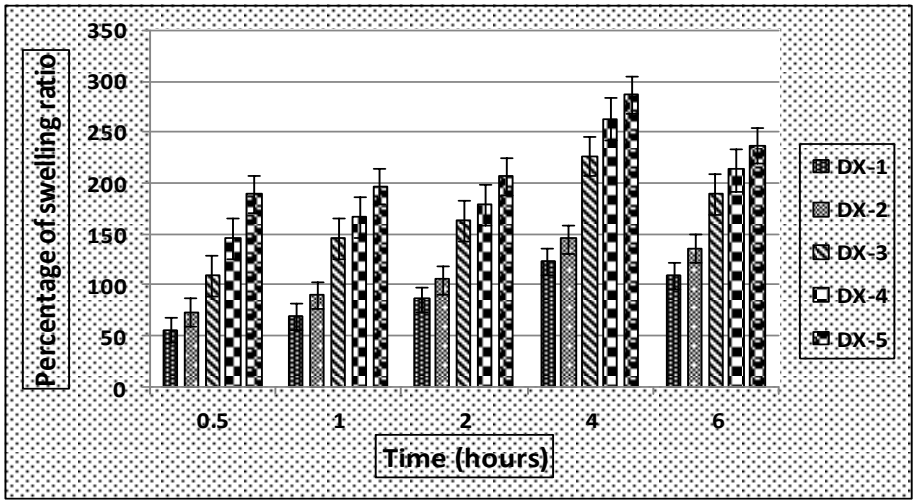


Figure 4 Effect of HPMC K15M and Pharmatose 200M on swelling behaviors of dexibuprofen matrix tablets in pH 6.8 PBS

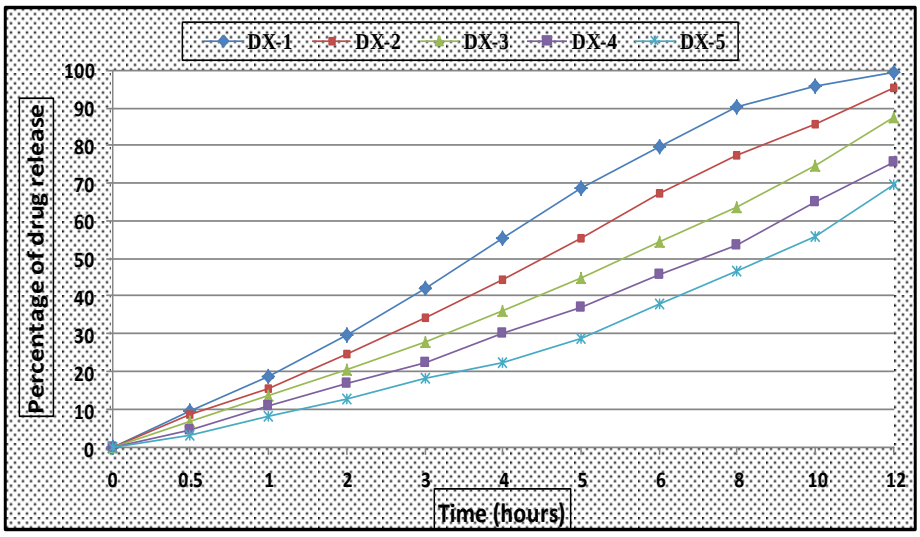


Figure 5. Effect of HPMC K15M and Pharmatose 200M on *in-vitro* drug release profiles of formulated matrix tablets of dexibuprofen

Effect of Kollidon SR and Pharmatose 200M

Table 3; explains that the weight variation of the matrix tablets observed within pharmacopeia limit of all the formulations were complied with the specifications given in I.P below ± 5% w/w of standard deviation from the average. However, the average weight of the matrix tablet of the batch DX-9 was obtained very nearer to theoretical weight. This indicates that the weight variation of formulated dexibuprofen tablets influenced by both polymer and diluent content. The hardness of the tablets obtained within acceptable range (< 6.0 kg / cm2) followed by decreasing the percentage of friability except the batch DX-6 because of low concentration of Kollidon SR used in the formulation decreases the mechanical strength due to less binding with high concentration of diluent (Pharmatose 200M).The percentage of

dexibuprofen content present in the tablets was found in the range of 90.26 ± 0.92 to 98.92 ± 0.88 respectively. It illustrates that the percentage of drug content influences mainly by increasing the concentration of Kollidon SR which entrapped more quantity of drug due to plastic deformation during compression and forms dense matrices.

The percentage of swelling ratio increases with increasing the concentration of both polymer and diluent ratio and observed in the range 155.40, 215.10, 258.40, 286.10 and 255.50 at the end of 6h **(Figure 6).** The formulation DX-6 containing higher level of Pharmatose 200M (above 200mg) and lower level of Kollidon SR shows higher swelling in initial hours followed by erosion at the end of 6h because Pharmatose 200M is more water-soluble excipient which helps to rapid hydration of polymer and erosion. The formulation of batch DX-10 containing more concentration of polymer and less concentration of diluent decreases the swelling due to low hydration of Kollidon SR. The formulation DX-9 shows steady state swelling ratio for 6 hours **(Figure 6).** This is due the presence of Pharmatose 200M enhance the formation of thick polymeric gel which acts as a barrier to penetrate water into interior boundary surface of tablet and gradually swells with an increasing time period.

Figure 7; illustrates that the percentage of dexibuprofen release from the matrix tablets in SGF pH 1.2 was obtained in the range of 37.52, 33.52, 29.65, 27.52 and 13.87 for initial 2 h. This may be due to poor solubility of dexibuprofen in this environment. On other hand, The percentage of dexibuprofen release in SIF of pH 7.4 in the range 91.20, 85.60, 79.35, 74.15 and 55.25 at the end of 12 h. The rapid drug release was observed from the batch DX-6 due to lower concentration of Kollidon SR as retardant. The formulation DX-10 containing high level of Kollidon SR and low level of Pharmatose 200M shows higher burst release in initial hours and the drug release may be attributed for the dissolution of water soluble povidone molecules which are components of Kollidon SR create pores and channels, thus facilitating solvent front penetration and elevation of drug release. Polyvinyl acetate (PVA) is a component of Kollidon SR not soluble in water and does not impede diffusion of drug from the matrix system and causes inefficient drug release for extended time period.[20] The formulation batch DX-4 containing optimum concentration of Kollidon SR and Pharmatose 200M shows a remarkable sustained release effect because Pharmatose 200 M is more water-soluble excipient, forms more micro-cavities in polymer matrices, forms dense matrix and influences swelling of matrices to form a thick polymeric gel layer. Moreover, this thick gel layer acts as surface barrier, controls the burst release of drug in lower pH level and followed

by control the release of drug in a sustained manner at higher level pH environment for a longer period of time.

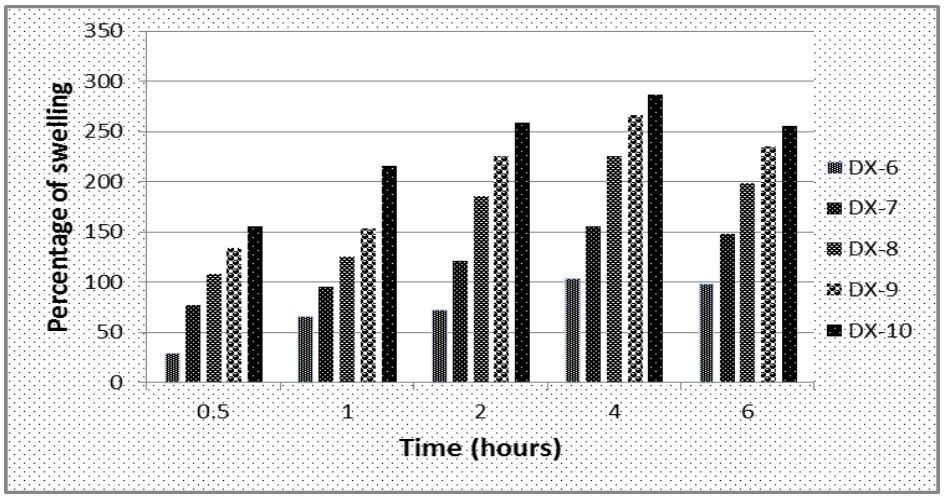


Figure 6. Effect of Kollidon SR and Pharmatose 200M on swelling behaviors of dexibuprofen tablets in pH 6.8 PBS

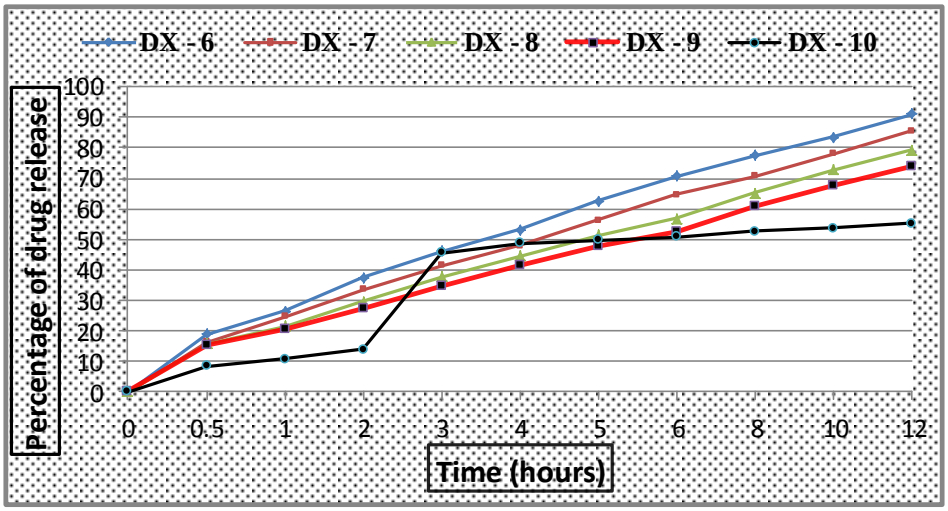


Figure 7. Effect of Kollidon SR and Pharmatose 200M on *in-vitro* drug release profiles of formulated matrix tablets of dexibuprofen

Analysis of various drug release kinetics

The in-vitro drug release of all the batches of DX-1 to DX-10 dexibuprofen matrix tablets was treated with various kinetic models. The mechanism of drug release was determined by using PCP-DISSOv2.08 software. The in-vitro drug release pattern of the formulated batches DX-1 to DX-5 were found to be highest correlation co-efficient (r2) in the range of 0.9908, 0.9897, 0.9918, 0.9983, 0.9979 corresponding to zero-order kinetics followed to Korsemeyer – Peppas model with good linearity of coefficient of correlation (r2) in the range of 0.9936, 0.9902, 0.9898, 0.9920, 0.9848 and diffusion coefficient (n) values are 0.8548, 0.8769,

0.9016, 1.0526, 1.1358 respectively (Table 4). The formulations DX-6 to DX-10 shows very good linearity to first order and obtained highest regression coefficient (r) values in the range of 0.9911, 0.9666, 0.9691, 0.9801 and 0.7845 followed to huguchi matrix with correlation coefficient (r2) values shows in the range of 0.9821, 0.9765, 0.9771, 0.9787 and 0.9132. The regression coefficient (r2) values of Korsemeyer – Peppas model obtained in the range 0.9779, 0.9732, 0.9708, 0.9699, 0.9162 and the diffusion coefficient (n) values are obtained 0.7189, 0.7246, 0.7732, 0.6381 and 0.6951 respectively (Table 4). The obtained data realizes that the release mechanism from the batches of DX-1 to DX-10 matrix tablets showed highest correlation co-efficient corresponding to zero-order followed to krosemeyer – peppas model and diffusion co-efficient (n) values found in the range of 0.8306 to 1.1358.This is because the higher swelling properties of HPMC K15M forms a thick polymeric gel, diffuses the drug gradually in a sustained manner. The formulation batches of DX-6 to DX-10 shows the mechanism of drug release both first order and huguchi matrix followed to krosemeyer - peppas mixed order kinetics. The formulation batches of DX-9 containing more concentration of Kollidon SR and less amount of diluent show highest correlation coefficient linearity to first order release mechanism due lower swelling properties of polymer. The diffusion co-efficient (n) values were observed from the batches DX-6 to DX-10 in the range of 0.6381 to 0.7246 **(Table 4).** This indicates, the drug release from matrix tablets by both diffusion and erosion mechanisms followed by Fickian matrix diffusion.

Table 4: *In-vitro* drug release of dexibuprofen matrix tablets fitted with various kinetic models

Batch code	Various Kinetic Models								
	Zero-order		First order		Huguchi matrix		Korsmeyer-peppas equation		
	r^2	K_0 (h^{-1})	r^2	K_1(h^{-1})	r^2	KH($h^{-1/2}$)	r^2	K_{KP} (h^{-n})	n-values
DX1	0.9908	8.6333	0.8833	-0.2273	0.9457	23.6658	0.9936	11.8389	0.8548
DX2	0.9897	8.2053	0.9087	-0.1839	0.9424	22.4720	0.9902	10.8145	0.8769
DX3	0.9918	7.7563	0.9406	-0.1519	0.9357	21.1649	0.9898	9.6602	0.9016
DX4	0.9983	7.0480	0.9552	-0.1231	0.9217	19.0454	0.9920	6.4918	1.0526
DX5	0.9979	6.5794	0.9469	-0.1094	0.9152	17.7230	0.9848	5.1901	1.1358
DX6	0.8731	9.2628	0.9911	-0.1875	0.9821	26.5012	0.9779	18.0268	0.7189
DX7	0.8654	8.6334	0.9666	-0.1609	0.9765	24.7119	0.9732	16.6485	0.7246
DX8	0.8866	8.0719	0.9691	-0.1401	0.9771	23.0088	0.9708	14.2140	0.7732
DX9	0.9015	7.5528	0.9801	-0.1216	0.9787	21.4720	0.9699	11.7707	0.6381
DX10	0.7192	6.3683	0.7845	-0.0899	0.9132	18.5553	0.9162	12.9978	0.6951

Where K_0 is zero order proportionality constant, r^2 is the regression coefficient; K_1 is the first order release rate constant, K_H is the Higuchi constant, K_{KP} is Peppas equation constant. n = Diffusion exponent related to mechanism of drug release, according to equation $M_t/M=K_{tn}$

CONCLUSION

In the present research work, the compressed tablet properties such as percentage of drug content, hardness, average weight and weight variation obtained an acceptable range and the values meet pharmacopeias limits. The swelling behaviors of formulated tablets remarkably increase with optimum proportion of polymer and diluent level. The optimum proportion of HPMC K15M and Pharmatose 200M (DX-4) shows the gradual swelling behavior and gives a great contribution to sustain the drug release for extended period of time. The formulation containing higher concentration kollidon SR as hydrophobic retardant and lower level of Pharmatose 200M (DX-10) shows low swelling behavior which effects on irrelevant drug release from the matrix tablets corresponding to specified time period. The in-vitro drug release significantly decreases with variable concentration of polymer and diluent ratio. The formulated drug loaded matrix tablets in SGF pH 1.2 show less than 20% w/w of drug release due to hydrophobicity of drugs, but maximum amount of drug release (>60 %w/w) in pH 7.4 at 6 h followed by sustaining up to 12 h. The kinetic drug release mechanism of optimized dexibuprofen matrix tablets of batch DX-4 was found to be linear and close correlation with huguchi matrix diffusion followed to Korsmeyer and Peppa's model and good regression co-efficient was observed due to diffusion and erosion mechanism of polymeric chains and shown the diffusion co-efficient (n) values in the range of 0.8548 to 1.1356. This indicates, the drug release from matrix tablets by both diffusion and erosion mechanisms followed by super case-II transport. Based on the investigated results, it was concluded that the polymer and diluent ratio modify the release of drug in different environmental pH conditions, capable of exhibiting to sustained release properties, environmentally stable and feasible for further scale up industrial production.

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