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Instamodel for the study of the impact of matrix dosage forms on the release of diclofenac sodium

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Abstract

Instamodel is a polymer that is used in the formulation development of matrix based tablet as sustained release drug delivery system includes all the dosage forms formulated to retard the release of the therapeutic agent such that its appearance in the systemic circulation is delayed and/or prolonged and its plasma profile is sustained in duration the onset of drugs pharmacologic action is often delayed and the duration of drugs therapeutic effects is sustained. Now a day, matrix and micro encapsulation is the most frequently employed method of producing sustained release dosage forms. Over the few decades' enormous progress has been made in developing these two technologies and applying it to diverse field of medical and other usage. In the following article mode formulation and various other evaluation parameter are discussed and finally shown the effect of their concentration on the drug release profile.

Keywords: Therapeutic agent, Matrix, Micro encapsulation, Sustained release, Retardant material

Introduction

The matrix system is most frequently applied among the innumerable methods used in controlled release of drugs from a Pharmaceutical dosage form. It involves the compression of blends of drug, retardant material and additives to form a tablet in which drug is embedded in a matrix core of the retardant[1]. Oral route is most widely used for matrix system but other routes are also adaptable. The release kinetics is accordance to Higuchi equation. These have linear release rate as a function of square root of time. Recent trends in sustained release drug delivery systems[2, 3].

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Material and methods

Diclofenac sodium fromVama pharma, Nagpur. Concentrated sulphuric acid and Concentrated Hydrochloric acid from Samara chemicals, Nagpur Starch, Lactose, Isopropanol Magnesium stearate from S.D. Fine Chemicals, Mumbai, Instamodel from Ideal cures, Mumbai, Microcrystalline Cellulose , Potassium dihydrogen phosphate and Sodium hydroxide from Loba Chemicals, Mumbai. Instruments: Double beam spectrophotometer(Shimadzu, 1601, Japan), Dissolution test apparatus(USP XXIV Veego Scientifics), Fourier transform infra red spectroscopy (FTIR) 8001, Shimadzo, Japan. Digital pH Meter (Elico Pvt. Ltd.,), Single Punch Tablet machine (Kulburn Monesta), Magnetic stirrer (Remi Electronics, India, Ltd.,), Tablet Hardness Tester (Monsanto), Roche friabilator (Elico Pvt. Ltd).reparation of matrix tablets Matrix tablets of diclofenac sodium were prepared by two different methods like direct compression and wet granulation by using various drug : Polymer ratios viz. 1:20, 1:40, 1:60, 1:80 1:1. Instamodel was used as matrix formulating material while lactose was used as diluent. Magnesium stearate was incorporated as Lubricant. The lubricated formulations were compressed in a single punch machine [model kulburn monesta] using 8 mm concave faced punches. Diclofenac sodium, instamodel are mixed with lactose for 10 minutes in polybag. All the ingredients were passed through a # 100 sieve. Then magnesium stearate was added as a lubricant and mixed for 5 min in a poly bag. The lubricated formulations were compressed by a direct compression technique using single punch hand operated machine fitted with 8 mm concave faced punches. Diclofenac, instamodel and lactose were mixed for 10 min in a polybag and then the blend was transferred into mortar. Isopropanol was gradually added to the mixture and the wet mass was prepared with hand.[4, 5] The wet mass was passed through #14 screen and wet granules was spread on flat paper and to drying in an oven at 150ºC for 4 to 6 hrs. The dried granules was passed through a # 18 screen and mixed with magnesium stearate as a lubricant for 5 min in a poly bag. Then finally the granules of diclofenac sodium were compressed by a single punch hand operated machine fitted with 8 mm concave faced punch.

Evaluation of Physical Properties of drug Loaded Granules[6, 10, 11] **(**Gibson 1989, Williams,.C et.al 2003, **USP, NF** 2007, . Lachman. L 3rd Edition) **Flow properties[1]:** (Brahmankar. D.B & Jaiswal. S.B 1995) 10 gm of sample powder is filled in funnel. Then funnel was opened to release the powder on the paper to form a smooth conical heap, is found by measuring in different direction. The values of angle of repose are calculated by using the following formula: $\tan \Theta = h/r$ or $\Theta = \tan^{-1} h/r$ Where, h- height of the heap, r- Radius of the heap. **Bulk density:** [6]A known quantity of powder was poured into the measuring cylinder carefully level the powder with out compacting, if necessary and read the unsettled apparent volume, Vo, to the nearest graduated unit . Calculate the bulk density, in gm per ml, by the formula m/Vo. **Tapped density[1]:** (Brahmankar. D.B & Jaiswal. S.B 1995) Cylinder dropping distance: 14 ± 2 mm at a normal rate of 300 drops / minute. **Measurement of Powder Compressibility:**

Compressibility index: $=100\ \frac{(V_0 - \overline{f})}{V_0}$ **Hausner Ratio:** $=Vf$

Compatibility studies[2] (Dyed. J.R 1965, Peter Tudja 2001) Thermogravimetric analysis: Losses of masses that occurred due to heating were determined under conditions that gave maximum noticeable degradation during TGA studies. About 4-6mg of the substance were placed in open platinum pan, heated at 1^0c/min within the range of 100- 850^0c under the dynamic flow of N_2 or synthetic air (20ml/min) and the loss of mass recorded. Fourier Transform Infrared Spectroscopy (FTIR): Compatibility study of drug with excipients was determined by I.R Spectroscopy using Shimadzu Fourier-transform infrared (FTIR-8400 S). The pellets were prepared at high compaction pressure by using KBr and the ratio of sample to KBr is 1:100. The pellets thus prepare were examined and the spectra of drug and the other ingredients in the formulation were compared with that of the original spectra. Evaluation of Matrix Tablets Weight variation*:* Twenty tablets were randomly selected and weighed to determine the average weight and were compared with individual tablet weight. The percentage weight variation was calculated. As per Indian Pharmacopoeia Specification, tablets with an average weight the percentage deviation should not more than ± 7. 5 % and tablets with an average weight more than 250 mg should not be more than ± 5 %. Friability Test: Weighed amount of 20 dedusted tablets were subjected to rotating drum of friability test apparatus. The drum rotated at a speed of 25 rpm. The apparatus was operated for 4 minutes and reweighedthe tablets. Friability was calculated by the followingformula.

$$F = 100 \left[\frac{W_o - W}{W_o} \right]$$

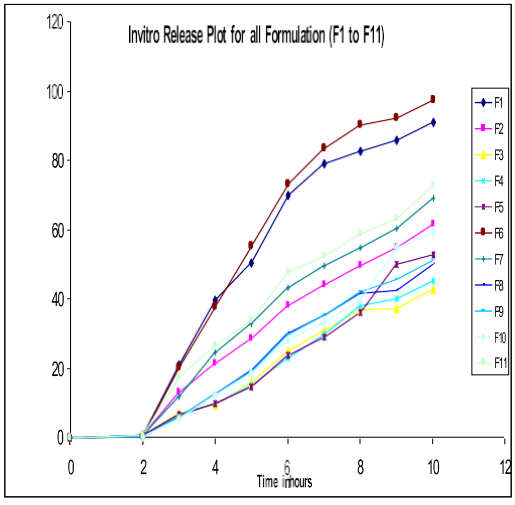
F = Friability, Wo = Initial weight, W = Final weight

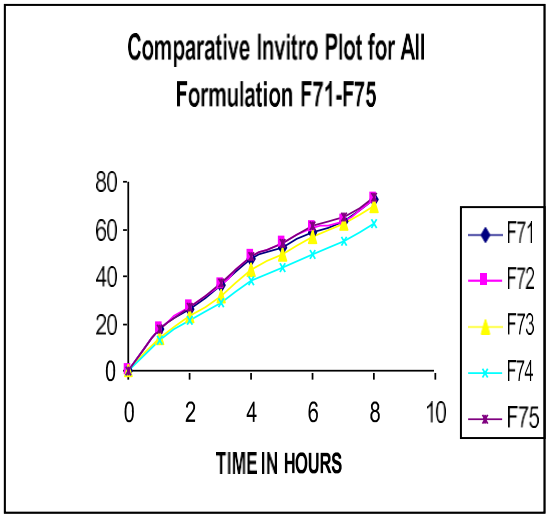
Hardness Test: The hardness of tablet was carried out by using Dr. Schleuniger type hardness tester. Drug content: 20 tablets were weighed accurately and powdered. Powder equivalent to 50 mg of diclofenac sodium was shaken with 60 ml of methanol in a 200 ml volumetric flask and diluted to volume with methanol. 5 ml of this solution was diluted to 100 ml with methanol and absorbance was measured at about 276 nm. The content was calculated from the absorbance obtained by repeating the procedure using diclofenac sodium in place of the substance being examined. Swelling Behavior of Matrix Tablets [12] (Yeole. P.G. et.al 2006) the extent of swelling was measured in terms % weight gain by the tablet. The swelling behavior of formula F7 was studied on tablet from the formulation was kept in a Petri dish containing pH 6.8 phosphate buffer. At the end of 1 hr, the tablet was withdrawn, soaked with tissue paper and weighed. Then for every 1 hr, weight of the tablet were noted and the process was continued in the end of 8 hr. % weight gain by the tablet was calculated by formula: S.I. = $[(M_t - M_0)/M_0] \times 100$, Where , S.I. = Swelling index, M_t = Weight of tablet at time ts, M_0 = Weight of tablet at time t = 0. Dissolution Study parameters: The dissolution test for diclofenac sodium matrix tablets prepared by two different methods was performed in triplicate using USP 24 paddle (Type II) method. The paddle was rotated at 50 rpm and the dissolution medium was maintained at 37 + 1^oC for 10 hours. 0.1 N HCl (pH 1.2) was used as dissolution medium for the first 2 hr, followed by phosphate buffer (pH 6.8) for further 8 hours[10, 11]. From this 5 ml of sample was withdrawn on every hour, and the same volume was replaced.5 ml of sample was made up to 25 ml with pH 6.8 phosphate buffer to maintain the perfect sinkcondition and the drug absorbance was measured at wavelength at 276 nm using a double beam spectrophotometer and data was calculated. At specified time withdrawn required amount of sampleand take absorbance and calculate percentage release. From the results of physical parameters and in vitro drug release studies of all prepared matrix tablets (Batches F1 to F11), we concluded that the Formula F7 (matrix tablet prepared by wet granulation) was found to be optimum for both physical characterization and in vitro drug release and also near by same release pattern was found with marketed SR diclofenac sodium matrix tablet of (F11) of Novarties Pharmaceuticals (Voveran SR). Stability Studies of Optimized Batches[7, 9] (F71 And F75) (Marcel Dekker 2nd edition, Indian Pharmacopoeia 1985, Silverstain .R.M 5th Edition). The effect of temperature and humidity (40 C and 75 °
% RH) on in-vitro drug release of the most promising formulation batches F71 and F75 was performed at every 15 days up to 60 days.

Results and Conclusion

Compatibility Studies FTIR Studies: The results of

FTIR studies are shown. From the results it was concluded that there were no changes in the peak shape and no shift of peaks. So the drug was compatible with the polymer (Instamodel). TGA studies: The results of TGA studies are shown. The onset of melting started at 26i0c for pure drug and 257.39 ^{0}C for best formulation. Both the drug and the best formulation are stable below 260 ^{0} C stable thermo gram will be observed. The loss of masses occurred during 261 to 277 ^{0}C in pure drug and 257 to 278.18^{0}c in best formulation. So it was concluded that there were no significant changes occurred in drug and the excipients. The loss of masses or degradation starts nearly at same temperature in pure drug and in best formulation. So the drug was compatible with the excipients. Flow Property: Results of Angle of repose, bulk density, tapped density; % compressibility and Housner ratio of diclofenac sodium granules are summarized in Table. Poor compressibility was observed in case of F1 and F10. All the other batch granules have passable flow ability and good compression properties. No color changes in granules were observed indicating that active ingredients and excipients were stable during granulation. Physical Parameters of Tablet: The tablet weight, hardness (range of 4-6kg/cm^2), friability values and drug content were found to be within the I.P limits. Swelling Behavior of Matrix Tablet: The swelling index of F7 batch was calculated with respect to time. As the time increases, the swelling index was increased. The direct relationship was observed between swelling index and instamodel concentration and as the polymer concentration increases swelling index. *In Vitro* Drug Release: The result was found that the all formulation showed very low drug release in 0.1N hydrochloric acid buffer (pH 1.2). This was due to the low solubility of Diclofenac Sodium at pH 1.2. Sustained, but complete release was displayed by allformulation in Phosphate buffer (pH 6.8). Thus it can be concluded, that drug dissolution was a function of drug solubility, at various pH ranges. Physical Properties of Drug Loaded Granules of Optimized Batch [F71-F75]: All the optimized batch granules have good flow property and good compression properties. Comparison of Formulation Batch F7 and F75 with Marketed Product (Voveran): We found that the release pattern of two batches was similar to that of marketed formulation release profile. The film coated formulation F75 provide better release pattern than the marketed preparation. So the film coated formulation F75 was found to be stable and better than other. Stability Studies of Film Coated Tablet F71 and F75: The effect of temperature and humidity on *invitro* drug release of the mostpromising film coated batch F71 and F75 was performed. No significant variation (1 to 3 %) in drug release was observed. Therefore itwas concluded that the batch F71 and F75 were stable over the chosen temperature and humidity for 2 months.





Graph: 1 **Graph: 2**

Diclofenac sodium sustained release matrix tablets was successfully formulated by using the instamodel (Drug: polymer). First order release of diclofenac sodium was achieved by instamodel in the ratio 1:40 [Drug: polymer]. All the formulation batches fulfill the I. P. limit for physical parameters like weight variation, hardness, friability and drug content uniformity. The in-vitro drug release studies indicted that the optimum release profile was found by formulation batch F71 and F75. The interesting highlights of our research are that the prepared sustained release formulations of diclofenac sodium matrix tablet using instamodel may be formulated using various other polymers through different techniques. The exploited part of in-vivo evaluation and their correlation with the marketed formulation will opens up a new channel in the drug delivery system.

Table: 1

Physical Evaluation of Diclofenac Sodium Granules

Table: 2

Batch No.	Weight Uniformity (in mgs)*	Hardness (Kg/cm^2)**	Friability± (in %)	Content uniformity (%)
F71	218± 0.62	5.28± 0.06	0.42± 0.06	97.03± 0.92
F72	215± 0.65	5.26± 0.12	0.48± 0.10	96.8± 0.70
F73	202± 0.90	5.23± 0.12	0.55± 0.04	96.8± 0.77
F74	202± 0.17	5.20± 0.14	0.45± 0.12	96.96± 0.54
F75	214± 0.33	5.20± 0.08	0.42± 0.07	96.05± 0.40

Physical Parameters of Prepared Matrix Tablet

Batch No.	Angle of repose	Bulk Density (gm/ml)	Tapped Density (gm/ml)	% Compressibility	Housner ratio
F_1	35.55 ± 0.53	0.80± 0.03	0.87± 0.05	11.9± 0.35	1.36± 0.22
F_2	36.32 ± 0.79	0.83± 0.01	0.69± 0.01	17± 0.69	1.20± 0.29
F_3	36.59 ± 1.54	0.74± 0.01	0.80± 0.03	10.8± 1.36	1.12± 0.27
F_4	37..33± 2.00	0.66± 0.02	0.63± 0.015	13.15± 0.78	1.16± 0.32
F5	36.43± 0.82	0.76± 0.08	0.83± 0.06	20.08± 1.12	1.25± 0.33
F6	35.76± 1.32	0.69± 0.01	0.82± 0.021	11.16± 0.98	1.12± 0.25
F7	37.19± 0.77	0.60± 0.20	0.71± 0.04	7.68± 1.20	1.08± 0.20
F8	36.32± 0.43	0.52± 0.07	0.76± 0.08	10.08± 0.72	1.10± 0.38
F9	36.79± 1.20	0.54± 0.018	0.80± 0.12	23.53± 0.85	1.30± 0.34
F10	36.49± 0.68	0.60± 0.02	0.79± 0.024	33.33± 0.12	12± 0.36

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