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FORMULATION AND *INVITRO* EVALUATION OF DELAYED RELEASE MICROPARTICLES OF DICLOFENAC POTASSIUM

N.Narayanan*, B.Tholkappiyan, A.Charles Martin, M. Gulshad, P.B Maheshwari, S. Preethirmayee

Department Of Pharmaceutical Analysis, Sri Lakshmi Narasimha College Of Pharmacy,S.F.316, Chittoor- Vellore Highway, Palluru, Chittoor-517312, (A.P), India

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Diclofenac potassium, delayed release micro particles, enteric coatings, anti-inflammatory activity, used in treatment of rheumatoid arthritis

For Correspondence:

B.Tholkappiyan

Sri Lakshmi Narasimha College Of Pharmacy, Palluru, Chittoor, A.P., India

E-mail:
tholsrmch@yahoo.com

ABSTRACT

In the present study, it was aimed to formulate delayed release Diclofenac potassium micro particles, which will have enteric release as well as sustained release properties. Diclofenac potassium is an effective non-steroidal anti-inflammatory drug used in symptomatic treatment of rheumatoid arthritis. The most common side effect of NSAID is a propensity to induce gastric ulceration. Hence, there is a potential need for enteric release dosage form for this drug. Delayed release micro particles of Diclofenac potassium was prepared by using cellulose acetate phthalate as the retardant polymer by emulsion solvent evaporation method. The drug and the polymer were dissolved in an organic solvent mixture (acetone and methanol). This solution was then emulsified into liquid paraffin and the organic solvent evaporated by stirring at room temperature for five hours to form micro particles. The micro particles were collected by filtration washed with hexane and dried at room temperature. It was also aimed to incorporate other modern enteric polymers such as Hydroxyl Propyl Methyl Cellulose Acetate Phthalate ($HPMCP_{55}$) and to study their influence on drug release rate from Cellulose Acetate Phthalate (CAP) micro particles of different batches were formulated. The micro particles were studied for their physico-chemical properties and invitro drug release.

INTRODUCTION:

Diclofenac potassium is an effective non steroidal anti-inflammatory drug used in symptomatic treatment of rheumatoid arthritis. The delayed release dosages from releases the active drug at a time other than promptly after administration. Inherent in the design of delayed release dosage form is a location or site specificity in drug release. An enteric coated tablet is an example of delayed release dosage form from which the drug is not immediately released in the stomach but is released when the dosage form is in the small intestine. To decrease the dependence on gastric emptying time and PH of the gastric contents and to minimize variability between doses, enteric coated granules have been formulated to disperse in the stomach and pass easily into the duodenum. Delayed release micro particles containing Diclofenac potassium was prepared by emulsion solvent evaporation method. Cellulose acetate phthalate was used as the main retardant polymer. The drug dissolved in solvent, emulsified, evaporated at room temperature; the formed micro particles were collected. Then the evaluation of physico-chemical properties of the micro particles is done. In the literature survey, found that R.S.R.Murthy, Saroj Bala et al, synthesized cellulose acetate maleate (CAM), the CAM coated sodium-bicarbonate tablets showed satisfactory core coat adhesion acid resistance and no drugs lose or coat disintegration in gastric media

S.M.Samant, R.P.Mahendra, S.M.Pradhan and H.P.Tipins performed an 8x5 complete cross over bioequivalence study in eight human volunteers using four different Diclofenac sodium enteric coated tablet formulations along with standard enteric coated formulation. All the test formulation was compared with standard by statistical pooled-test to prove their bioequivalent characteristics.

Diclofenac potassium has analgesic, antipyretic and anti-inflammatory activities. Also reduce intracellular concentrations of free arachidonate in leukocytes, perhaps by altering the release or uptake of fatty acid. It is ideally suited for patients on sodium free diet, hypertensive patients, to treat painful inflammatory conditions of patients on diuretic therapy. It is used in conditions such as rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and acute gout. Also used for the short term treatment of acute musculoskeletal injury, acute painful shoulder, dysmenorrhoea and dental pain. Diclofenac is also used as

0.1% eye drops for the inhibition of intraoperative miosis (but it does not possess intrinsic mydriatic activity) and to prevent post operative inflammation in cataract surgery. The most common side effect of NSAID is a propensity to induce gastric or intestinal ulceration and leads to blood loss sometimes enteric coating is known to be the best approach to prevent or minimize such side effect.

In the present study it was aimed to formulate delayed release Diclofenac potassium micro particles, which will have enteric as well as sustained release properties. For the preparation of Diclofenac potassium micro particles, cellulose acetate phthalate and hydroxyl propyl methyl cellulose phthalate were used as coating materials. Among the prepared micro particles, the best formulation is reported by invitro release studies.

MATERIALS

Methanol AR and Acetone AR were purchased from SD Fine chemicals, Mumbai. Diclofenac Potassium gift sample brought from the Madras Pharmaceuticals, Chennai and also Cellulose Acetate Phthalate obtained from Tablets India Ltd., and Hydroxyl Propyl Methyl Cellulose Acetate Phthalate sample brought from Tablets India Ltd., chennai

METHOD:

Delayed release micro particles containing Diclofenac potassium was prepared by emulsion solvent method. Cellulose acetate phthalate was used as the main retardant polymer.

PREPARATION OF DELAYED RELEASE MICROPARTICLES OF DICLOFENAC POTASSIUM

The drug (0.3g) was dissolved in 10% w/v solution of cellulose acetate phthalate (in acetone methanol 8:2 solvent mixture). This was then emulsified onto liquid paraffin and the organic solvent evaporated by stirring at the room temperature for 5hrs to form cellulose acetate phthalate micro particles containing the drug. The micro particles formed were collected by filtration, washed with hexane and dried at room temperature.

COMPOSITION OF DIFFERENT DELAYED RELEASE MICRO PARTICLES:

Table1:

Sl. No	Drug	Liquid paraffin (ml)	Solvent		CAP (gm)	Hp (gm)
			Acetone	Methanol		
1	0.3	100	8	2	1.0 (10%)	-
2	0.3	100	8	2	0.8 (08%)	0.2 (2%)

EVALUATION:-

DRUG CONTENT ANALYSIS:-

100mg of micro particles of the 30/40 mesh size was accurately weighed and

shaken with 20ml of Ethyl acetate to dissolve the wall material and the drug was extracted with 10 portions of distilled water. From the pool of 50ml, 2ml was taken and made up to 100ml and from that 1ml was pipette out in 10ml standard flask. To this 0.5ml of 1% potassium ferric cyanide and 0.2% of 6% NaOH were added and set aside for 1 minute, for the development of yellow color and it was made to 10ml with distilled water absorbance was measured at 450nm. Concentration of the drug was calculated from the standard graph.

DRUG CONTENT OF DELAYED RELEASE MICRO PARTICLES:-

Table2:

Batch code	Drug content
F_1	20.5
F_2	20.0

DETERMINATION OF THE PERCENTAGE OF DRUG ENTRAPPED IN THE MICRO PARTICLES

This was carried out to find out the percentage of drug entrapped in the micro particles. The following formula was used:

$$\text{Percentage drug entrapped} = \frac{\text{(Amount of drug in micro particles per gm)}}{\text{(Amount of drug used per gm)}} \times 100$$

The results are shown in the following table:-

PERCENTAGE OF DRUG ENTRAPPED IN MICRO PARTICLES OF DIFFERENT BATCHES

Table3

Batch code	Drug content	% of drug entrapped	Percentage of drug left entrapped
F_1	20.5	89.11	10.99
F_2	22.5	97.80	2.20

INVITRO EVALUATION:-

DRUG RELEASE STUDY:-

Invitro release profile of Diclofenac potassium from micro particles was examined in P^H 1.2 buffer from 0 to 2 hrs and in 7.2 P^H buffer 2 to 8 hrs by rotating basket method specified in USP xx1 at 100 rpm using 900 ml of test fluid maintained at 37^0C. Micro particles retained on sieve no: 40 were taken for release study. Micro particles equivalent to 100 mg of Diclofenac potassium was accurately weighed and placed in the 40 meshes basket. The basket was rotated at about 100rpm. At suitable intervals 2ml aliquot was removed. The same volume of fresh test fluid was added to the test medium to maintain the original volume. The drawn 2 ml samples were made up to 10 ml.

From this, 1 ml was with drawn and to that 1% w/v potassium ferric cyanide and 6% w/v NaOH were added and made up to 10ml and the concentrations of the drug were determined calorimetrically at 450nm. The results were reported. The percentage of Diclofenac potassium released at various time intervals was calculated and plotted against time.

KINETICS OF DRUG RELEASE:-

The order of drug release can be assessed by graphical treatment of drug release data. A plot percentage of drugs remaining versus time would be linear, if the drug release follows zero order kinetics (i.e. concentration independent release)

The linear equation for zero order drug release plot is

$$C_t = C_0 - kt$$

Where C_t = conc. remaining at time t

C_0= original conc.

T = time

K = release rate

A plot of drug of percentage of drug remaining versus time would be linear, if the drug release follows first order (i.e. conc. dependent release)

The linear equation for first order drug release plot is

$$\text{Log } C = (\log C_0) \times ((kt)/ (2.303))$$

Since the polymers used for preparing micro particles are soluble in the medium, it was assumed that the drug release may follow first order. So the drug release data obtained in dissolution studies for all batches were treated according to first order equation by plotting log cumulative percentage drug remaining against time.

Invitro drug release to Diclofenac potassium from micro particles prepared from CAP Dissolution medium hydrochloride acid buffer (P^H 1.2) for first two hrs and Phosphate buffer (P^H 7.2) thereafter.

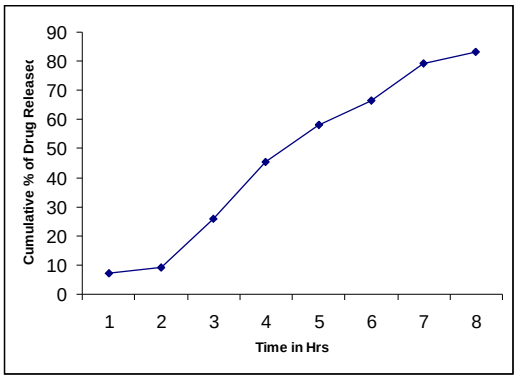
Table4:

Batch code F_1

Time	Cumulative amount of drug released(mg/ml)	Cumulative percentage of drug released	Percentage of drug remaining to be released	Log Percentage of drug remaining to be released	$(1-M_t/M)^{1/3}$
1	7.2	7.2	92.80	1.9675	0.9753
2	9.08	9.08	90.80	1.9580	0.9687
3	25.83	25.83	74.17	1.8702	0.9051
4	45.22	45.22	54.78	1.7386	0.8182
5	58.07	58.07	41.93	1.6225	0.7484
6	66.46	66.46	33.54	1.5255	0.6947
7	79.41	79.41	20.59	1.3136	0.5904
8	83.38	83.38	16.00	1.2206	0.5498

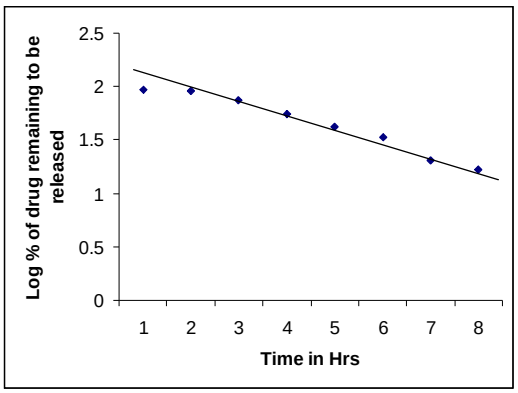
PLOT SHOWING RELATION BETWEEN CUMULATIVIE % AMOUNT DRUG RELEASED Vs TIME FROM MICROPARTICLES PREPARED FROM CAP

(BATCH CODE – F_1)



PLOT SHOWING RELATION BETWEEN LOG % OF DRUG REMAINING TO BE RELEASED Vs TIME FROM MICROPARTICLES PREPARED FROM CAP

(BATCH CODE – F_1)



PLOT SHOWING RELATION BETWEEN $(1-M_t/M)^{1/3}$ Vs TIME FROM MICROPARTICLES PREPARED FROM CAP

(BATCH CODE – F_1)

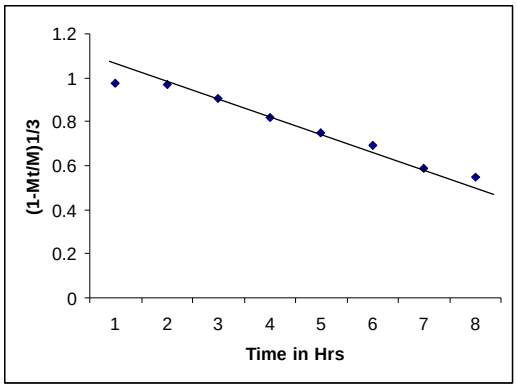


Table5:

Invitro drug release of Diclofenac potassium from micro particles from CAP and $APMCP_{55}$

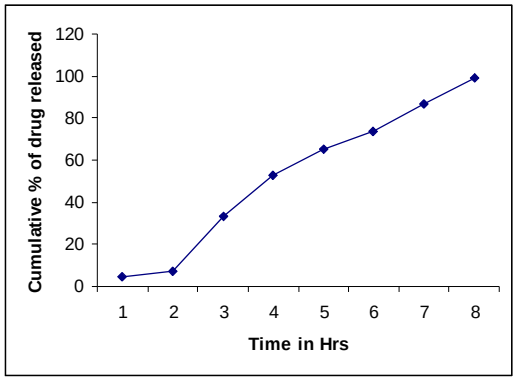
Dissolution medium hydrochloric acid buffer (p^H 1.2) for first two and phosphate buffer (p^H 7.2) thereafter.

Batch Code: F_2

Time	Cumulative amount of drug released (mg/ml)	Cumulative percentage of drug released	Percentage of drug remaining to be released	Log percentage of drug remaining to be released	$(1-M_t/M)^{1/3}$
1	4.5	4.5	95.5	1.9800	0.9847
2	7.262	7.262	92.738	1.9672	0.9751
3	33.04	33.04	66.96	1.8258	0.8748
4	52.64	52.64	47.36	1.6754	0.7794
5	65.49	65.49	34.51	1.5379	0.7014
6	73.88	73.88	26.12	1.4169	0.6392
7	86.83	86.83	13.17	1.1195	0.5087
8	98.97	98.97	1.03	0.0128	0.2175

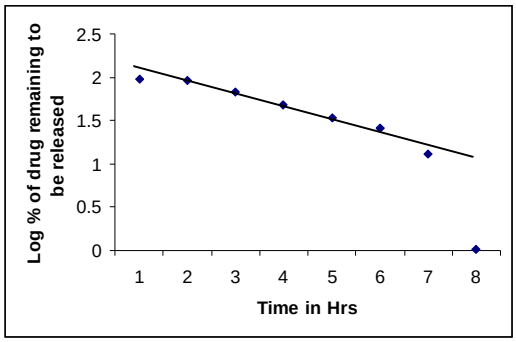
PLOT SHOWING RELATION BETWEEN CUMULATIVE % AMOUNT OF DRUG RELEASED Vs TIME FROM MICROPARTICLES PREPARED FROM CAP AND HPMCP

(BATCH CODE – F_2)



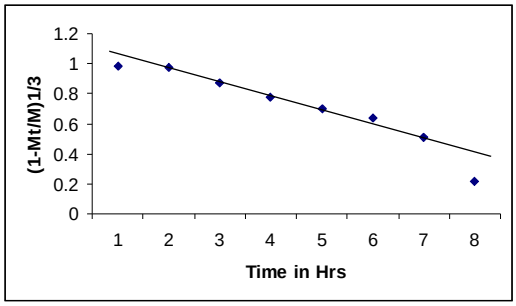
LOT SHOWING RELATION BETWEEN LOG % OF DRUG REMAINING TO BE RELEASED Vs TIME FROM MICROPARTICLES PREPARED FROM CAP AND HPMCP

(BATCH CODE – F_2)

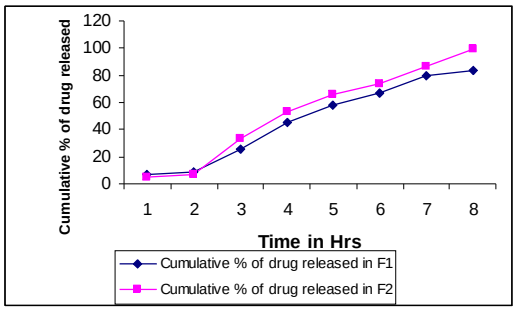


PLOT SHOWING RELATION BETWEEN $(1-M_t/M)^{1/3}$ Vs TIME FROM MICROPARTICLES PREPARED FROM CAP AND HPMCP

(BATCH CODE – F_2)



COMPARITIVE STUDY OF CUMULATIVE % AMOUNT OF DRUG RELEASED Vs TIME BETWEEN F_1 AND F_2



SIZE ANALYSIS:-

Size analysis of all batches of prepared micro particles were carried out using a set of standard sieves ranging from 10-80 mesh.

SIZE ANALYSIS OF MICRO PARTICLES:

Table 6:

BATCH CODE F_1:-

Sieve passed/retained	Sieve opening in µm	Arithmetic mean size of opening in µm	Weight retained on smaller sieve in gm	% retained on smaller sieve	Weight size	Average diameter in µm
10/20	2000/840	1420.0	0.0132	1.19550	1697.610	364.50
20/30	840/590	715.0	0.1121	10.15670	7252.040	
30/40	590/420	505.0	0.2014	18.24770	9215.080	
40/50	420/297	358.5	0.3201	29.00244	10397.370	
50/60	297/250	273.5	0.0232	2.10200	574.897	
60/70	250/210	230.0	0.1341	12.15000	2794.500	
70/80	210/177	193.5	0.0723	6.55060	1267.540	
80/100	177/149	163.0	0.1782	16.14560	2631.730	
100/ 120	149/125	137.0	0.0491	4.44860	609.450	
			1.1037	99.9991	36450.220	

The sieves were arranged in decreasing order of mesh size (i.e.) 10 mesh on the top and 120 mesh at the bottom. The micro particles were passed through the set of sieves and amount retained on each sieves is weighed.

The arithmetic average diameter was determined by dividing the total weight size by 100.

Results given in table, in order to determine the size distribution analysis was carried out by plotting.

Fig.4a. SIZE DISTRIBUTION ANALYSIS BATCH CODE

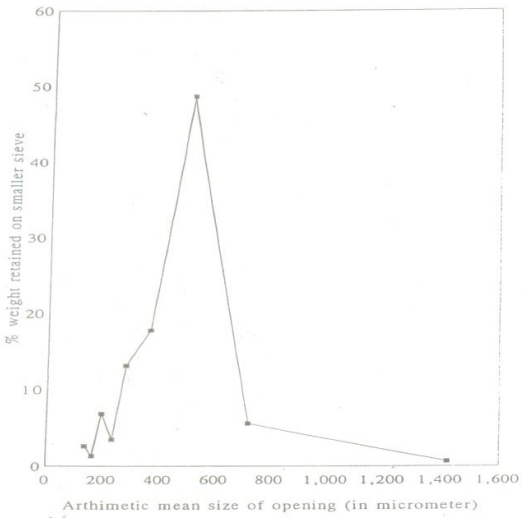


Fig.4b. SIZE DISTRIBUTION ANALYSIS BATCH CODE

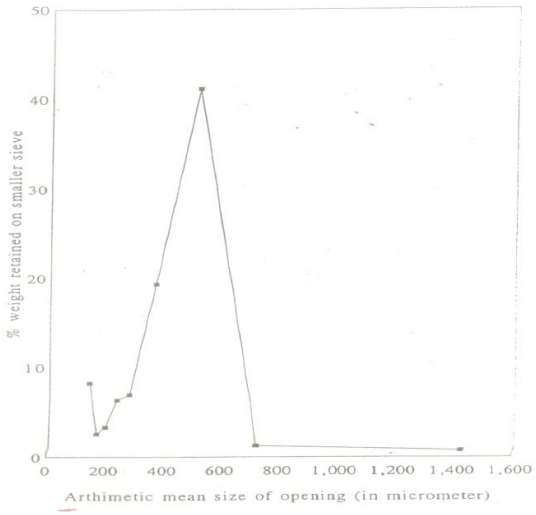


Table7:

BATCH CODE F2:-

Sieve passed/ retained	Sieve opening in micro meter	Arithmetic mean sized openings in micro meter	Weight retained on smaller sieve in g	% retained on smaller sieve	Weight size	Average diameter in micro meter
10/20	2000/840	1420.0	0.0211	0.7668	1088.85	
20/30	840/590	715.0	0.0354	1.2865	919.84	
30/40	590/420	505.0	1.1321	41.1433	20777.3	
40/50	420/297	358.5	0.5312	19.3051	6920.87	
50/60	297/250	273.5	0.1917	6.9668	1905.41	352.72
60/70	250/210	230.0	0.1752	6.3672	1464.45	
70/80	210/177	193.5	0.0917	3.3326	644.85	
80/100	177/149	163.0	0.0712	2.5875	421.76	
100/120	149/125	137.0	0.502	8.2439	1129.41	
			2.7516	99.9997	35272.41	

EVALUATION OF PHYSICO CHEMICAL CHARACTERISTICS OF MICRO PARTICLES

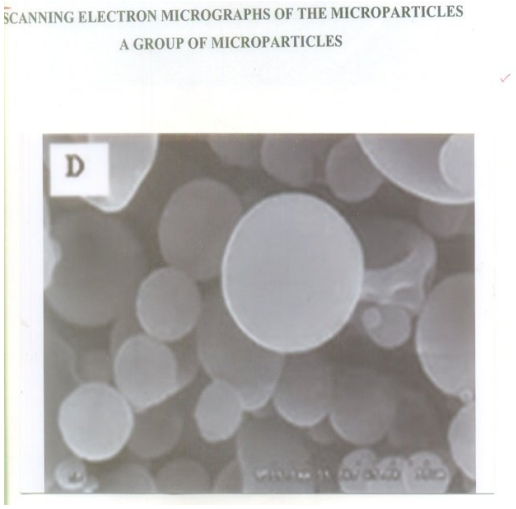
The prepared micro particles were spherical in shape with free flowing in nature. To study the physico chemical characteristics the following evaluation is done.

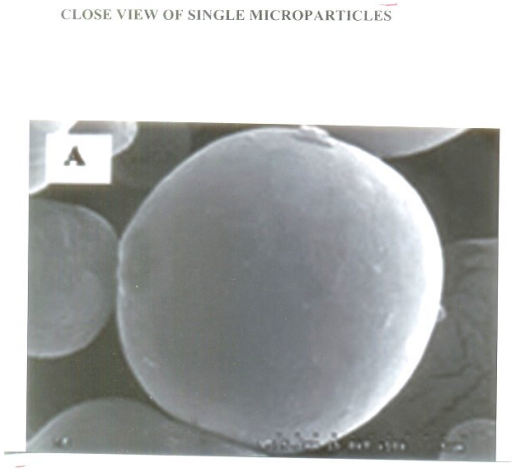
a. Melting point:-

Small amount of micro particles were taken and they were ground to remove the coating material and then subjected to melting point test. It showed the same melting point as that of pure sample of Diclofenac potassium.

b. Morphology:-

The morphology of micro particles was examined by scanning electron microscope (SEM) at different magnifications. It was found that the micro particles are spherical in shape.





RESULTS AND DISCUSSION

The aim of the present work is to prepare delayed release micro particles of Diclofenac potassium. The micro particles were prepared by emulsion solvent evaporation technique. Cellulose acetate phthalate was used as the main retardant polymer for p^H dependent release of Diclofenac potassium from micro particles. The influence of other polymers such as hydroxyl propyl methyl cellulose phthalate on the drug release from CAP micro particles was also examined.

The polymer and drug were dissolved in an organic solvent mixture. This solution was then emulsified into liquid paraffin and the solvent was allowed to evaporate at room temperature. The system was stirred continuously. The micro particles formed were collected by filtration. They were evaluated for morphology, melting point, size analysis, drug content uniformity and invitro drug release.

MORPHOLOGY:-

Scanning electron micrographs of the prepared micro particles reveal that they are discrete and spherical in shape.

MELTING POINT:-

The melting point of the micro particles was carried out to find it there is any change in the nature of the encapsulated drug.

The micro particle showed the same melting point as that of the pure sample of Diclofenac potassium.

SIZE DISTRIBUTION:-

The log normal size distribution was observed in all batches of micro particles prepared.

DRUG CONTENT AND PERCENTAGE DRUG ENTRAPPED:-

Micro particles were tested for the drug content uniformity. The drug content was found to be good and the drug Diclofenac potassium was found to be encapsulated above 80% in almost all batches of micro particles, which shows that there is no wastage of drug and hence this method is economical regarding encapsulation efficiency.

INVITRO DRUG RELEASE STUDY:-

The dissolution study was carried out in p^H 1.2 buffers for the first two hours in phosphate buffer of p^H 7.2 for the remaining time to evaporate at room temperature.

BATCH F_1:-

The data for the preparation of Diclofenac potassium micro particles by using CAP (Cellulose Acetate Phthalate) alone is presented in table – 3.

The following modes of data treatment are done.

1. Cumulative percent of drug release versus time.
2. Log percentage of drug remaining to be released versus time.
3. Erosion equation $(1-M_1/M)^{1/3}$.

The results showed that the drug release in the first two hours (i.e.) in acidic buffer is negligible. This is due to the fact that CAP is insoluble in the acidic P^H. from the third hour onwards P^H 7.2 buffer was used. The release is considerable at the end of the eight hour 83.38% when a plot is made between cumulative percentages of drug release versus time, according to zero order equation there is no linearity.

But a plot of log cumulative percent of drug remaining versus time showed linearity. This shows that the drug released followed first order kinetics. This proves that the drug release from micro particles is concentration dependent. The plot of $[1-M_1/M]^{1/3}$ versus time was found to be linear, which indicates the main mechanism of drug release is erosion.

BATCH F_2:-

The data for the preparation of Diclofenac potassium micro particles using a combination of CAP and $HPMCP_{55}$ is presented in table.

As expected, the drug release in the acidic medium for the first two hours was found to be negligible. This is due to the fact that both the polymers are insoluble in

acidic P^H. the drug release in the remaining period in the phosphate buffer was found to follow first order kinetics.

Erosion was found to be the mechanism of release from the linear expression of the release data in the plot of $[1-M_1/M]^{1/3}$ versus time. The drug release was found to be greater than that of the previous batch F_1. This drug release was found to be almost 96.95% at the end of 8 hours. This may be due to the fact that $HPMCP_{55}$ is more rapidly soluble than CAP at P^H 7.2.

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