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Formulation and evaluation of controlled drug release naproxen pellets

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ABSTRACT

The ultimate dosage forms for pellets can be capsule or they may be compressed into disintegrating tablets. Interest in this area has been increasing continuously, since it offers some important pharmacological as well as technological advantages. Extrusion -Spheronization may be defined as a process in which a wet mass is extruded through a specific sieve with fixed diameter and subsequently spheronized into spherical particle called as spheroids, pellets or beads depending upon materials and process used for Extrusion –Spheronization. Controlled release pellets have minimum volume in size, greater surface area and more surface activity. The area of the drug loaded pellets release rate was also more. And also there was no need of disintegration time for pellets in capsules. Small volumes of pellets enter into the systemic circulation very fast. Moreover there was no accumulation of drug in the body. Drug release rate was more when compared with that of other formulations. Naproxen controlled release pellets were filled into capsules. It showed good results in formulation of stable dosage. The dissolution profile was determined for all the formulations. Formulation F9 was considered as optimized formulation in terms of percentage cumulative drug release, coating build up, chanelling agent ratio etc.

Keywords: Pellets, Dissolution rates, Naproxen.

INTRODUCTION

Controlled drug delivery systems have been developed which are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity and/or targeting the delivery of drug to a tissue [1]. Controlled delivery can be defined as [2] Sustained drug action at a predetermined rate by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects [2]. Controlled Drug Delivery System avoids patient compliance problems, Dosage frequency were reduced [3]. The method pelletization technique was developed in the early 1960s and since then has been researched and discussed extensively. Intrest in the technology is still strong, as witnessed by the extent of coverage of the topic in scientific meetings and symposium proceedings, as well as in scientific literature [4]. Pellets are agglomerates of fine powders or granules of bulk drugs and excipients. They consist of small, free-flowing, spherical or semi-spherical solid units, typically from about 0.5 mm to 1.5 mm, and are intended usually for oral administration. Implants of small, sterile cylinders formed by compression from medicated masses are also defined as pellets in pharmacy [5]. The investigated the possibility of producing alginate-

based pellets by extrusion-spheronization and also to improve the formation of spherical alginate-based pellets by investigating the effect of additive in granulation liquid on characteristics and drug release from resulting pellets [6]. The microcrystalline cellulose extrusion-spheronization pellets as means of increasing the dissolution rate of hydrochlorothiazide [7]. The information of pellet structure is not finished before drying stage [8].

MATERIALS AND METHOD

Table 1: Materials used for the formulation development

S.No	Ingredients
1	**Naproxen**
2	MSicrocrystalline cellulose (avicel PH 101)
3	Hydroxypropyl cellulose(Klucel)
4	Opadry Clear
5	Ethylcellulose (Ethocel)
6	Hydroxyl propyl methyl cellulose

Table 2. List of equipment's

S.No	Equipments
1	Electronic balance
2	Rapid mixer granulator
3	Extruder
4	Spheronizer/Marumerizer^{TM}
5	Rapid dryer
6	Mechanical stirrer
7	Fluid bed coater
8	Mechanical sieve shaker
9	Dissolution apparatus
10	UV-Visible spectrophotometer
11	Tapped density apparatus USP
12	FTIR

FORMULATION DEVELOPMENT

Preparation of pellets

Granulation

Naproxen, microcrystalline cellulose (avicel PH 101), hydroxy propyl cellulose (klucel) were passed through 30# mesh, and the sifted material was transferred into rapid mixer granulator (Kelvin). Then the material was allowed for dry mixing for 10 min by using impeller speed of 150 RPM and water was added for 3 min till the formation of granules. Chopper was run for 3 min at 1000 RPM to complete the granulation process.

Preparation of pellets

The granules were passed through Fuji Paudal extruder using 0.8 mm screen at 40 RPM, the obtained spaghetti like extrudates was collected and placed on Fuji paudal Marumerizer using 2mm plate.

Coating of pellets

Sub coating

Pellets were loaded into fluid bed wurster and initial subcoating was made with opadry clear at

The spheronizer was run at 800 RPM for 30 sec, 1800 RPM for 90 sec and 1300 RPM for 60 sec to get pellets of satisfactory sphericity. The pellets were collected and dried in rapid dryer at 45^0C for 2 hrs and then sized through 16/30 mesh [9]

4%build up. Polymer coating: polymer EC: HPMC coating was done in the ratio of 65:35 by giving 20% buildup to pellets [10].

ENCAPSULATION

The Individual weights of optimized pellets were taken and filled into capsules manually

Ingredient	F 1	F 2	F 3	F 4	F5	F6	F7	F8	F9	F10	F11
Core spheroids											
Naproxen (mg)	2	2	2	2	2	2	2	2	2	2	2
MCC (PH 101)	1.952	1.585	1.585	1.585	1.585	1.585	1.952	1.952	1.585	1.92	1.952
Lactose(Granular 200)	1.18	0.65	0.65	0.65	0.88	1.18	1.18	0.88	0.65	0.65	0.88
HPC(Klucel EXF)	0.11	0.07	0.11	0.07	0.11	0.11	0.07	0.11	0.07	0.07	0.11
Water QS											
Total core spheroids	**5.242**	**4.305**	**4.345**	**4.305**	**4.575**	**4.875**	**5.202**	**4.942**	**4.305**	**4.64**	**4.942**
Sub coat											
HPMC 4 cps	0.16	0.124	0.124	0.124	0.124	0.124	0.16	0.124	0.124	0.171	0.183
Talc	0.07	0.05	0.05	0.05	0.05	0.05	0.05	0.07	0.05	0.07	0.07
Total sub coated spheroids	**5.47**	**4.479**	**4.519**	**4.479**	**4.631**	**5.049**	**5.412**	**5.136**	**4.479**	**4.881**	**5.195**
EC coating											
Ethyl cellulose 20 cps	0.66	0.53	0.53	0.788	0.66	0.788	0.887	0.887	0.665	0.887	0.887
HPMC 4 cps	0.12	0.130	0.142	0.191	0.147	0.47	0.201	0.201	0.162	0.142	0.177
PEG 400	0.04	0.07	0.08	0.10	0.112	0.106	0.130	0.136	0.08	0.153	0.177
Total EC Coated spheroids	**6.29**	**5.209**	**5.271**	**5.558**	**5.55**	**6.413**	**6.636**	**6.36**	**5.386**	**6.063**	**6.436**

ANALYTICAL METHOD DEVELOPMENT

Preparation of standard calibration graph of Naproxen

Preparation of standard solution of Naproxen

Stock solution

25mg of Naproxen was weighed accurately and transferred into a 25 ml volumetric flask. Then the volume was made 25ml with Methanol.

Standard solution

10ml of solution was withdrawn from the above stock solution and then made upto 100ml in another 100ml volumetric flask with 7.4 pH Phosphate Buffer and this solution is considered as standard solution (100µg/ml).

- From the above standard solution 0.5, 1, 1.5, 2, 2.5ml was withdrawn and diluted to 10ml to get 5, 10, 15, 20, 25µg/ml concentration.
- The solutions were analysed spectrophotometrically at 231nm using UV visible spectrophotometer.

EVALUATION

Evaluation of Pellets

The pellets were evaluated for in process quality control test.
The following test were performed for ER pellets

Determination of Bulk Density and Tapped Density

An accurately weighed quantity of the granules/ powder (W) was carefully poured into the graduated cylinder and volume (V_0) was measured. Then the graduated cylinder was closed with lid and set into the tap density tester (USP). The density apparatus was set for 100 tabs and after that the volume (V_f) was measured and continued operation till the two consecutive readings were equal.

The bulk density and the tapped density were calculated using the following formulae.

Bulk density = W/V_0

Tapped density = W/V_f

Where, W= Weight of the powder

V_0 = Initial volume

V_f = final volume

Compressibility Index (Carr's Index)

Carr's index (CI) is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is.

Where, TD is the tapped density and BD is the bulk density.

Table 3. Carr's Index Values

S.No.	Carr's Index	Properties
1	5-12	Free flowing
2	13-16	Good
3	18-21	Fair
4	23-35	Poor
5	33-38	Very poor
6	>40	Extremely poor

Hausner's Ratio

It is the ratio of tapped density and bulk density. Hausner found that this ratio was related to interparticle friction and, as such, could be used to predict powder flow properties. Generally a value less than 1.25 indicates good flow properties, which is equivalent to 20% of Carr's index.

Particle size distribution:

100gms of pellets are shifted into a sieve shaker where a series of sieves was placed (16#, 22#, 25# and 30#). The machine was run for 5 minutes, all the meshes were taken out and retained granules were collected by respective mesh and the percentage retention of pellets by that mesh was calculated.

EVALUATION OF CAPSULES

Drug content estimation

Weigh and powder 20 capsules. Weigh accurately a quantity of powder containing equivalent weight of 5 capsules weight of Naproxen into a 100 ml volumetric flask. Dissolve with the aid of small quantities of methanol, make up to 100 ml with methanol and filter. Dilute 10 ml of filtrate to 100 ml with 7.2 phosphate buffer and mix. Pipette out 10 ml of solution into a 100 ml volumetric flask and make up to 100 ml with 7.4 phosphate buffer and mix. Measure the absorbance of the resulting solution at 231 nm in UV. Results are shown in Table no (9.9).

In vitro drug release Studies

In vitro drug release of the samples was carried out using USP-type I dissolution apparatus (Basket type). The dissolution medium, used was 7.4

phosphate buffer 900ml (as specified by the office of generic drugs USFDA), placed into the dissolution flask maintaining the temperature of 37±0.5°C. 2 mg Naproxen capsule were placed in each flask of dissolution apparatus. The apparatus was allowed to run for 20 hour at 50 RPM. Samples measuring 10ml were withdrawn at specified time intervals. The fresh dissolution medium was replaced every time with same amount of buffer. The samples were filtered and analyzed at 231 nm. The cumulative percentage drug release was calculated.

RELEASE KINETICS

The results of *in vitro* release profile obtained for all the formulations were plotted in modes of data treatment as follows.

1. Log cumulative percent drug remaining versus time (first order kinetic model)
2. Cumulative percent drug release versus square root of time (Higuchi's model)
3. Cumulative percent drug release versus time (zero order kinetic model)
4. Log cumulative Percent Drug released versus log time (Korsmeyer model)

Drug release kinetics-model fitting of the dissolution Data

Whenever a new solid dosage form is developed or produces, it is necessary to ensure that drug dissolution occurs in an appropriate manner. Drug dissolution from solid dosage forms has been described by kinetic models in which the dissolved amount of drug (Q) is a function of the test time, t or Q = f (t). Some analytical definitions of the Q (t) function are commonly used such as zero order, first order, Higuchi, korsmeyers-peppas models. Other release parameters, such as dissolution time ($t_{x\%}$), dissolution efficacy (ED), difference factor *(f_1)*, similarity factor *(f_2)* can be used to characterize drug dissolution / release profile.

Zero-order kinetics

A zero-order release would be predicted by the following equation.

$A_t = A_o - K_o t$ ……. eq (5)

Where, A_t = Drug release at time t
A_o = Initial drug concentration
K_o = Zero-order rate constant (hr)

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.

Use

This relation can be used to describe the drug dissolution of several types of modified release pharmaceutical dosage forms, as in case of some transdermal systems etc. the pharmaceutical dosage forms following this profile release the same amount of drug by unit of time and it is the ideal method of drug release in order to achieve a prolonged pharmacological action.

First-order kinetics

A first order release would be predicted by the following equation.

$\text{Log } C = \text{Log } Co - K_t / 2.303$ …….. eq (6)

Where C = Amount of drug remained at time t
C_o = Initial amount of drug
K = First-order rate constant

When the data is plotted as log cumulative percent drug remaining versus time yields a straight line indicating the release follows first-order kinetics, the constant k can be obtained by multiplying 2.303 with slope values

Use

- The pharmaceutical dosage forms containing water-soluble drugs in porous matrices, follows this type of dissolution profile.
- The release of the drug is proportional to the amount of drug remaining in its interior so that the amount of drug release by unit of time diminishes

Higuchi model

Drug release from the matrix devices by diffusion has been described by following higuchi's classical diffusion equation.

$Q = [DE/ \tau(2A- ECs) C_{st}]$ ..... eq (7)

Where,
Q = Amount of drug release at time t
D = Diffusion coefficient of the drug in the matrix
A = Total amount of drug in unit volume of matrix
C_s = The solubility of the drug in the matrix
E = Porosity of the matrix

T = Time in hrs at which q is the amount of drug is release

Equation-3 may be simplified if one assumes that D, Cs and A are constant. Then equation-3 becomes

$Q = K_t ½$ ……. eq (8)

When the data is plotted according to equation-4 i.e. cumulative drug release versus Square root of time yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equal to k.

Use: The relation can be used to describe the drug dissolution from several types of modified release pharmaceutical dosage forms, as in case of some water soluble drugs.

Korsmeyer Peppas model

In order to understand the mode of release of drug from swellable matrices, the data were fitted to the following equation

$$M_t / M_{\acute{a}} = Kt^n \cdots\cdots\cdots\cdots \text{eq (9)}$$

Where,

$M_t / M_{\acute{a}}$ = The fraction of drug released at time't'

K = Constant incorporating the structural and geometrical

Characteristics of the drug / polymer system.

n = Diffusion exponent related to the mechanism of release.

The above equation can be simplified by applying log on both sides we get

$$\text{Log } M_t / M_{\acute{a}} = \text{Log } K + n \text{ Log } t \ldots\ldots \text{ eq (10)}$$

When the data is plotted as a log of drug released versus log time, yields a straight line with a slope equal to n and the k can be obtained from y-intercept.

The value of n for a cylinder is <0.45 for fickian release, > 0.45 and < 0.89 for non-Fickian release, 0.89 for the case 2 release and > 0.89 for super case2 type release

RESULTS AND DISCUSSIONS

Standard Calibration Graph of Naproxen

Standard graph of Naproxen was prepared by taking 25mg of drug in 25ml of Methanol solution to get (1000µg/ml stock solution) from the above stock solution suitable dilutions were made to get 5,10,15,20,25 µg/ml solution and the absorbance was measured at 231nm in UV spectrophotometer. A graph was drawn by taking concentration on X axis and absorbance on Y axis. From the graph, the regression was found to be 0.9996. It obeys Beers law.

Table 4 Standard Calibration Curve

S.No	Concentration µg/ml	UV Absorbance at 231 nm
1	0 µg/ml	0.00
2	5µg/ml	0.183±0.02
3	10µg/ml	0.358±0.02
4	15µg/ml	0.536±0.02
5	20µg/ml	0.710±0.02
6	25µg/ml	0.891±0.02

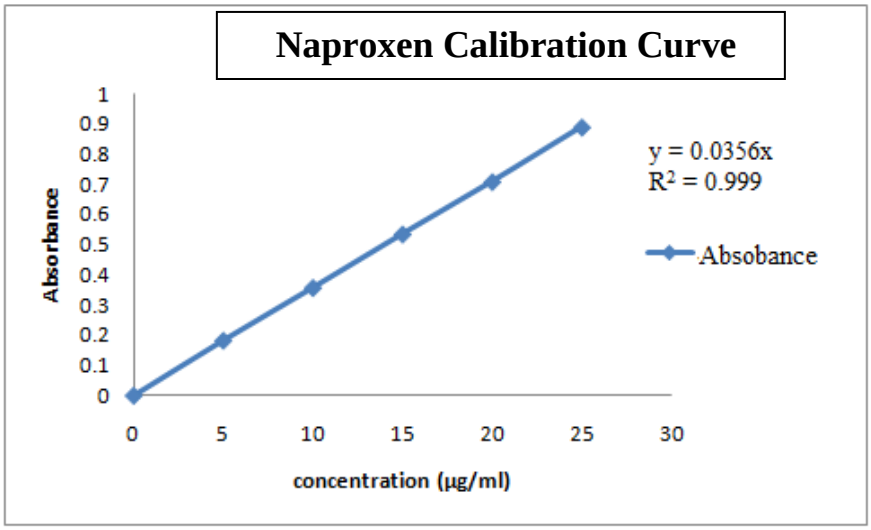

Fig.1.Standard Calibration Curve of Naproxen

Compatibility studies

The spectrum of the standard and the samples were then superimposed to find out any possible interactions between the drug and the polymers.

Characteristic peaks of Naproxen

Serial number	Wavelength	Specification
1	3344.3 (3300-3500) cm^{-1}	–NH stretch
2	2900.7 (2850 – 3000) cm^{-1}	(C-H) stretch
3	2900.7 (3300 - 2500) cm^{-1}	(O-H) stretch
4	1342.4 (1350 –1550) cm^{-1}	(N=O) stretch
5	1072.3 (1220 -1020) cm^{-1}	(C-N) stretch
6	1033.8 (1000 –1300) cm^{-1}	(C-O) stretch

FTIR Spectra of Naproxen

Pre-Formulation studies

Table 4 Bulk Density, Tap Density, Carr's Index, Hausner's Ratio of Naproxen Pellets

Formulation code	Bulk density (g/cc)	Tap density (g/cc)	Carr's Index (%)	Hausner's ratio
F1	0.234	0.220	3.54	0.56
F2	0.324	0.320	3.24	0.43
F3	0.236	0.356	2.93	0.45
F4	0.421	0.254	3.87	0.36
F5	0.286	0.296	4.12	0.78
F6	0.412	0.342	4.23	0.99
F7	0.221	0.456	3.56s	0.56
F8	0.332	0.451	4.56	0.68

F9*	0.61	0.592	5.71	1.06
F10	0.286	0.523	3.67	0.83
F11	0.312	0.561	3.12	0.41

Bulk density and tapped density values range between 0.446 – 0.480 gm/cc and 0.539 – 0.637g/cc tabulated and the values were found to be within limits

Compressibility index has been proposed as an indirect measure of bulk density, size, shape, surface area and cohesiveness of materials. Compressibility index values ranges between 5-12% for F1 to F11 formulations and the values are tabulated.

Hausner's ratio it is the ratio of tapped density and bulk density. Hausner found that this ratio was related to interparticle friction and, as such, could be used to predict powder flow properties. Generally a value less than 1.25 indicates good flow properties, which is equivalent to 20% of Carr's index.

Particle Size Distribution of Naproxen

Sieve number	% Cumulative retains
#16	0
#18	2.9
#20	31.0
#25	95.0
#30	100

Optimization of sub coating

Medium: Water
Volume: 900ml (Naproxen 2mg)
Apparatus: Basket (50 RPM)

Optimization of sub coating

Time (Hours)	% Drug Release			
	F8 (Without subcoating)	**F7 (3% sub coated)**	**F9 (5% sub coated)**	**F3 (7% sub coated)**
2	34	31	21	19
4	57	55	41	38
8	80	78	68	55
12	86	90	88	76
20	90	93	99	85

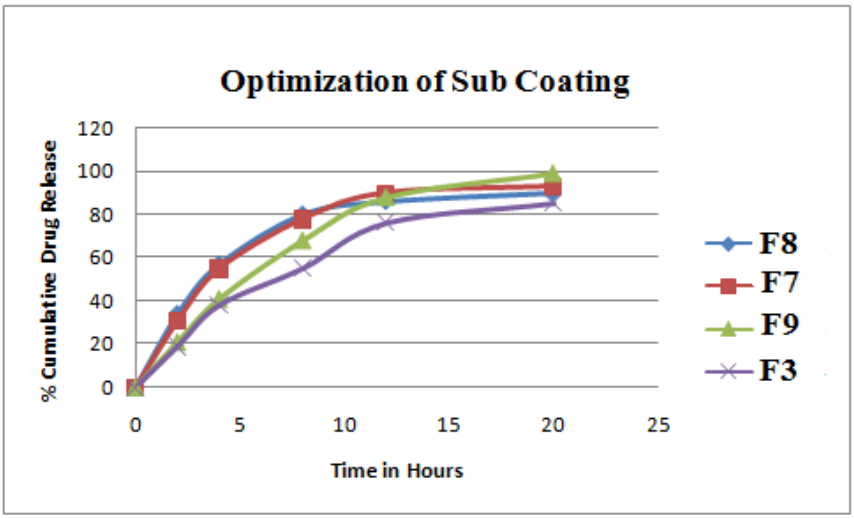

Fig.2 Dissolution Profile of Optimization of subcoating

It was observed that formulations (F7, F9, and F3) were sub coated with different concentrations of HPMC and the dissolution profiles were determined, formulation F9 showed better release profile compared with that of F7, F8 and F3, so formulation F9 was selected as the desired formulation with sub coating concentration of 5%.

Dissolution Profile

Time (hours)	Percentage Cumulative Drug release										
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
2	10	24	15	21	21	30	31	34	21	25	11
4	32	46	32	41	42	53	55	57	41	48	33
8	55	69	55	63	67	74	78	80	68	71	60
12	77	90	76	86	88	86	90	91	88	79	81
20	94	95	93	89	91	96	91	95	99	84	90

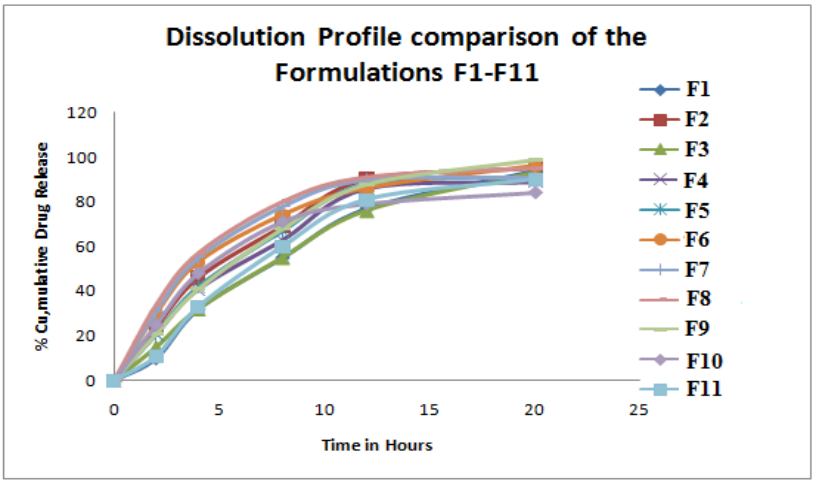

Fig. 3 Dissolution Profile comparison of all the formulations of pellets

Dissolution profile for the formulations (F1, F3 and F11) had poor dissolution profile, formulation (F9) showed good drug result when compared with other formulations, and so it had been selected as desired formulation for compressing into the tablet.

Kinetic studies of Naproxen Capsules

Release kinetics	R^2	Intercept	Slope
Zero order	0.934	10.49	3.29
First order	0.953	4.964	-0.14
Higuchi	0.934	11.0	25.61
Korsmeyer peppas	0.991	0.66	0.74

Dissolution- Zero Order kinetics

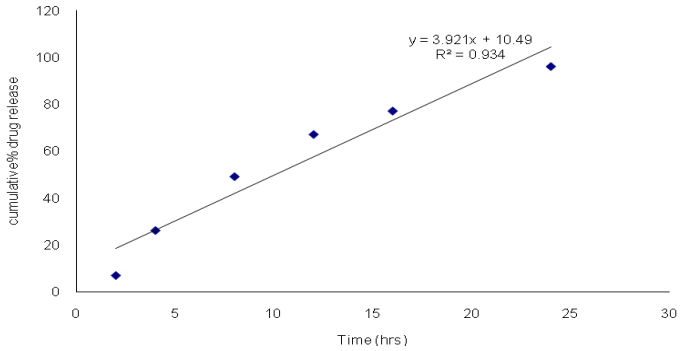

Fig 4 Graph for the formulation F9-Zero Order Kinetics

Dissolution- First order Kinetis

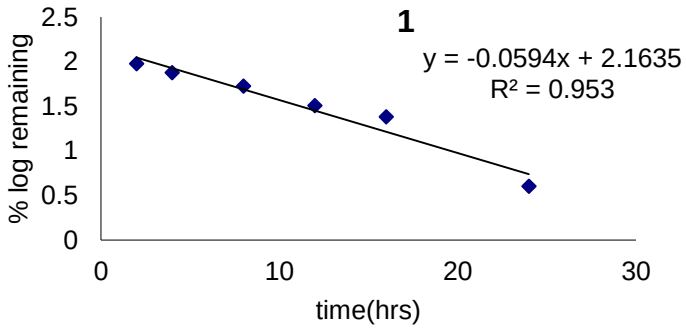

Fig: 9.7 Graph for the formulation F9-First Order Kinetics

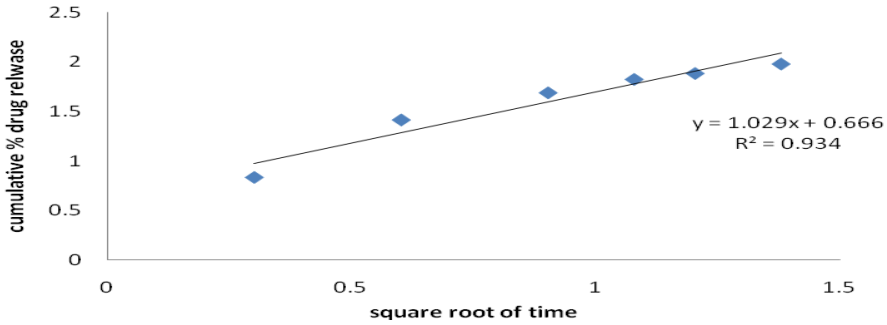

Fig 5 Graph for the formulation F9-Higuchi model

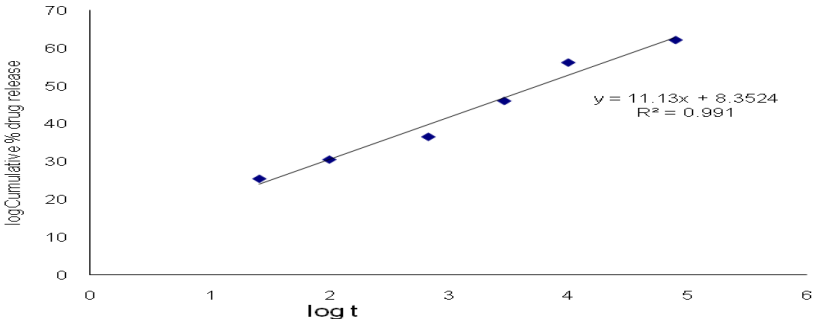

Fig 6. Drug Release Kinetic For F9 Formulation

The kinetic of drug release for formulation F9 was calculated and plotted. The formulation F9 follows first order release kinetics and the drug release mechanism was found to be non-Fickan anomalous diffusion.

CONCLUSION

Based on the literature search and reference product review, prototype development was initiated with preparation of core spheroids by extrusion spheronization technique and coating the spheroids with a controlled release rate controlling polymer by wurster process. The spectrum of the standard and the samples were then superimposed to find out any possible interactions between the drug and the polymers. All the characteristic peaks of Naproxen mentioned in were also found in the spectrum formulations. The results suggest that the drug is intact in the formulations and there is no interaction found between the drug and the excipients.

Spheroids with MCC concentration of 50% and 55% found satisfactory hence 55% has been finalized Spheroids with HPC concentration of 1% in core spheroids found satisfactory, hence it has been finalized Optimization of binder concentration was done with HPMC concentration of 0.5%, 1%, 0.7%. No much significant change is observed with change in binder concentration 0.5% is considered as optimum concentration Optimization of binder concentration was done with concentration of 3%, 5%, 7%.the formulation with 5% found satisfactory, hence it has been finalized. Optimization of controlled release coating builds up16% build up of EC/HPMC of formulation (F9). The result was found better to that of other formulations.

The pellets were analyzed for the parameters such as bulk density, tapped density, compressibility index, Hausner's ratio and the results were found to be within the limits.

Bulk density and tapped density values range between 0.446 – 0.480 gm/cc and 0.539 – 0.637g/cc tabulated and the values were found to be within limits Compressibility index has been proposed as an indirect measure of bulk density, size, shape, surface area and cohesiveness of materials. Compressibility index values ranges between 5-12% for F1 to F11 formulations and the values are tabulated. Hausner's

ratio it is the ratio of tapped density and bulk density. Hausner found that this ratio was related to interparticle friction and, as such, could be used to predict powder flow properties. Generally a value less than 1.25 indicates good flow properties, which is equivalent to 20% of Carr's index. Controlled release pellets have minimum volume in size, greater surface area and more surface activity. The area of the drug loaded pellets release rate was also more. And also there was no need of disintegration time for pellets in capsules. Small volumes of pellets enter into the systemic circulation very fast. Moreover there was no accumulation of drug in the body. Drug release rate was more when compared with that of other formulations.

The Naproxen controlled release pellets were filled into capsules. It showed good results in formulation of stable dosage. The dissolution profile was determined for all the formulations. **Formulation F9** was considered as optimized formulation in terms of percentage cumulative drug release, coating build up, chanelling agent ratio etc.

The kinetic of drug release for formulation F9 was calculated and plotted. The formulation F9 follows first order release kinetics and the drug release mechanism was found to be non-Fickan anomalous diffusion.

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