AMERICAN JOURNAL OF PHARMTECH RESEARCH
Journal home page: http://www.ajptr.com/

Multiparticulate Sustain Drug Delivery System of Flurbiprofen

Geeta M. Patel *, Tejas B. Patel
** Department of Pharmaceutics, Shree S. K. Patel College of Pharmaceutical Education and Research, Ganpat University, Kherva-384012, Gujarat, India*

ABSTRACT

The aim of this study was to develop a pH independent enteric coated extended release pellets containing flurbiprofen. The drug loaded pellets were prepared by using extrusion/ spheronization method using microcrystalline cellulose in combination with dicalcium phosphate dihydrate as pellet forming agents. Core pellets were coated with polymers Eudragit RS-100 and Eudragit RL-100 in a fluid bed coater to achieve a sustainable release for 24 hours. The pellets were subjected to physicochemical studies, SEM study, *in-vitro* drug release, kinetic studies and stability studies. DSC and FTIR studies shown there was no interaction between drug and polymers. The physicochemical properties of pellets were found within the limits. The drug release from the optimized formulations was extended for a period of 24 hrs i.e. first 2 hrs no drug release was observed and gradually drug release was increased up to 24 hrs. From the above results, achievement of site specific release to lower part of gastrointestinal tract might be due to Eudragit RL 100. The optimized formulation was subjected to stability studies and showed no significant changes in drug content, physicochemical parameters and release pattern. In conclusion, development of novel and good approach to achieve the site specific release of drug Flurbiprofen.

Keywords: Flurbiprofen, sustain drug delivery, site specific release, extrusion-spheronization.

*Corresponding Author Email: gmppharmacist@gmail.com
Received 12 August 2017, Accepted 27 November 2017

Please cite this article as: Patel GM *et al*., Multiparticulate Sustain Drug Delivery System of Flurbiprofen. American Journal of PharmTech Research 2017.

INTRODUCTION

Pellets are defined as small spherical or semispherical particles made up of fine powders or granules of drugs and excipients by a variety of processes **(**Erkoboni DF et al, 2010, Thommes M et al 2009)[1,2]. Their multiparticulate natures offer some important pharmacological, as well as technological advantages over conventional single-unit solid dosages including more stable plasma profiles, little risk of local side effects and dose dumping, improved bioavailability, good flow properties, and easy coating (Ghebre-Sellassie I et al, 1989)[11]**.** Various processes which can be utilized to prepare pellets are: extrusion–spheronization, powder/solution/suspension layering and melt extrusion. Extrusion–spheronization is a well-established process that has been described for obtaining pellets of high density, narrow size distribution and high drug loading **(**Erkoboni KA et al**,** 2003)[3].

In recent years, great efforts have been made to develop controlled drug release systems that achieve the optimum therapeutic effect of drugs; the drug concentration is maintained in the therapeutic window for a period of time, thereby ensuring sustained therapeutic action. There are very few extrusion aids available, out of which microcrystalline cellulose (MCC) is the most widely used extrusion aid because it has good binding properties and provides the necessary plasticity to the wet mass, which both ensure successful extrusion and spheronization (K.R. Zimm et al, 1996)[4].

In several diseases (such as bronchial asthma, hypertension, rheumatic disease and myocardial infarction) and for the control of body functions (blood pressure, and the levels of many hormones, e.g. aldosterone, renin and cortisol) influenced by circadian rhythms, delayed or pulsatile drug release could be the optimum approach. Pellets offer biopharmaceutical advantages in terms of more even and predictable distribution and transportation in the gastrointestinal tract, which is fairly independent of the nutritional state. The interest in pellets as a dosage form (filled into hard capsules) has increased continuously, for their multiparticulate nature offers important pharmacological and technological advantages over conventional single-unit solid dosage forms.

Flurbiprofen is a new non-steroidal anti-inflammatory agent, one of the propionic acid groups, which has significant anti-inflammatory, analgesic and antipyretic properties. Clinically, it is used for the treatment of rheumatoid arthritis, degenerative joint disease, osteoarthritis, ankylosing spondylitis, acute musculoskeletal disorders, low back pain and allied conditions. The absorption of flurbiprofen is rapid and almost complete when given orally. It is given orally as 150–200 mg daily in 3 or 4 divided doses and the biological half-life of flurbiprofen is about 4–6 h. In order to

remove or reduce the undesired secondary effects of flurbiprofen, and to prolong the short elimination half-life of conventional immediate release dosage forms of flurbiprofen, sustain release pellets is promising dosage form by reducing the frequency of administration, and improve patient compliance.

The present study is aimed at formulating sustained release coated pellets loaded with flurbiprofen using the extrusion/spheronization technique and coating technique (Gandhi R et al, 2007)[5].

MATERIALS AND METHOD

Flurbiprofen was generous gift from Shree Parikh Pharma (Ahmedabad, India). Microcrystalline cellulose PH 101 was received as gift sample from Acme Pharmaceuticals (India). Eudragit RL 100and Eudragit RS 100 was generous gift from Evonik Degussa India Pvt. Ltd. (Mumbai, India). Dicalcium phosphate dihydrate (DCPD), lactose, talc, acetone, isopropyl alcohol was purchased from Finar Chemicals Ltd, (Ahmedabad, India). All other ingredients were of laboratory grade.

EXPERIMENTAL METHODS

Drug-Excipients compatibility study

To check the compatibility of Flurbiprofen with other formulation excipients, DSC studies were performed.

Preliminary study

A preliminary study was set up to determine general formulation and processing parameters needed to prepare pellets using the extrusion spheronization process. Ultimately, further evaluations were made to facilitate improvements in both the formulations used and the processing conditions employed.

Various process variables in extrusion spheronization were studied and optimized to get uniform size, shape and yield of pellets (Baert J et al., 1993, Elbers J et al. 1992, Heng P. et al. 2001)[6-8]. Variable parameters for these preliminary trial batches are as follows.

Extruder screen size	: 0.50 mm, 0.87 mm
%LOD (Loss on drying) of extrudes	: 10%, 15%, 20%, and 25%
Spheronization time	: 120 sec, 180 sec, 300 sec, 420 sec.
Spheronization speed	: 300 rpm, 600 rpm, 1200 rpm, 1500 rpm

Preparation of core pellets

Water was used as a granulating liquid in the preparation of Flurbiprofen-loaded core pellets. Water functions as a moistening and binding agent in the wet massing stage, acts as a lubricant and plasticizer during the extrusion process, imparting plasticity during spheronization. It affects the

quality of extrudates and their ability to spheronize (Lustig-Gustafsson C et al., 1999). The amount of water was important to the process and the quality of pellets produced. Flurbiprofen and pellet excipients were mixed at certain weights and the powder mixture was wetted with water. Next, the resulting wet mass was extruded at a speed of 60 rpm with a screen pore size of 0.5 mm (Mini Extruder). Spheronization was performed in a mini spheronizer with a rotating plate of regular cross-hatch geometry, at a speed of 1200 rpm, for 300 seconds. Pellets were then dried on a tray in a hot oven at 50–60 °C for 2 hours. After drying, spherical particles were passed through Vibratory Sifter to achieve different size distribution.

Preparation of Flurbiprofen coated pellets

Core pellets were coated with polymers Eudragit RS 100 and Eudragit RL 100 in a laboratory fluid bed coater. Isopropyl alcohol, acetone and water were taken to prepare coating suspension. Eudragit RL 100 and Eudragit RS 100 were added slowly into the region of vortex with continuous stirring for approximately 30 min. Thereafter, talc as anti tacking agent and dibutylphthalate as a plasticizer was added into it with continuous stirring for approximately 30 min. The Flurbiprofen core pellets were coated using fluid bed processor with Eudragit RL 100 and Eudragit RS 100 containing coating suspension in a three ratio of 1:2, 1:1, 2:1 to a thickness equivalent to theoretical coating load 5% and samples were drawn for analysis. Machine parameters set up during coating of Flurbiprofen pellets are shown in table-1. Compositions of different pellet formulations are shown in table-2.

Characterization of Flurbiprofen coated pellets

Prepared pellets of Flurbiprofen were evaluated for the following parameters.

Percentage yield

The measured weight was divided by total amount of all non-volatile components which were used for the preparation of pellet.

% Yield = Total weight of excipients and drug / Actual weight of product x 100 ….(1)

Table 1: Machine parameters set up during coating

Parameters	Specifications
Spray gun nozzle diameter	1.0 mm
Silicon tube diameter (ID / OD)	2 mm
Atomizing air pressure	1.5±0.5 kg/cm^2
Inlet air temperature	45-60°C
Exhaust air temperature	50-60 °C
Product bed temperature	40°C
Inlet air humidity	50 -55 % RH
Spray rate	8 ml/min

Table 2: Compositions of different pellet formulations (%w/w)

Batch codes	FT1	FT2	FT3	FT4	FT5	FT6	FT7	FT8	FT9
Flurbiprofen	50	50	50	50	50	50	50	50	50
Micro crystalline cellulose	10	10	10	20	20	20	20	20	20
Dicalcium phosphate dihydrate	20	20	20	20	20	20	10	10	10
Lactose	20	20	20	10	10	10	20	20	20
MCC: DCPD	1:2	1:2	1:2	1:1	1:1	1:1	1:2	1:2	1:2

Drug Content

The drug content was measured by UV spectroscopic method. Content of Flurbiprofen was calculated at the specific absorbance at 247 nm.

Size of the pellets

Determination of average pellet size of Flurbiprofen pellet was carried out by using leica/optical microscopy (Rowe R.C et al. 2005)[9]. A minute quantity of pellet was spread on a clean glass slide and average size of 20 pellets was determined in each batch.

Flow properties of pellets

The flow properties of the pellets were studied by measuring the Carr's index and angle of repose of pellets.

Friability

An accurately weighed amount of pellets, about 6 g, was taken and placed in a friability tester and tumbled for 200 revolutions at 25 rpm. Twelve steel balls (diameter 6 mm, weighing 0.884 g each) were included as attrition agents. After friability testing, the pellets were sieved through sieves mesh # 16, # 20, # 40, # 60 and retained on mesh # 100 (200μm aperture size). The friability of pellets was calculated as:

$$\% \text{ Friability} = W_i - W_r / W_i \times 100 \quad \text{.....(2)}$$

Where, *Wi* is the initial weight of pellets before friability testing, and *Wr* is the total weight of pellets retained above the sieve (mesh # 100) after friability testing.

Hardness of pellets

Hardness of pellets was measured by using digital Phrmatest hardness tester. 5 numbers of pellets from each batch were used for hardness measurement. Triplicate trials were taken for measurement of hardness of pellets.

In-vitro dissolution study

In vitro dissolution profile of each formulation was determined by employing USP I rotating basket method (900 ml of 0.1 N HCl, 50 rpm at 37±0.5 ^{o}C, for 2 hr ; 900 ml of pH 6.8-phosphate buffer, 50 rpm and 37±0.5 ^{o}C, for subsequent hrs up to 24 hrs) (Sousa J. J et al., 1996)[10]. Pellets

equivalent to 200 mg of Flurbiprofen fill into hard gelatin capsule. Capsule was loaded into the basket of the dissolution apparatus. Sample aliquots of 10 ml were withdrawn at suitable time intervals and the same amount was replaced with fresh media each time. The sample solution was filtered through a whatman filter (0.45 µm membrane) paper, diluted suitably and absorbance was measured at 247 nm by using Shimadzu 1700 UV–Vis spectrophotometer, against dissolution media as blank.

Scanning electron microscopy (SEM)

Morphological characteristics of pellets were observed by scanning electron microscopy (SEM). It has been used to determine particle size distribution, surface topography, texture and examine the morphology of fractured or sectioned surface.

3.5.9 Stability Studies

The stability studies of optimized batch of pellets were carried out for six weeks at different accelerated conditions like 2-8 °C, 25 °C / 60 %RH and 40 °C / 75 %RH. The samples were analyzed for assay of the Flurbiprofen.

RESULTS AND DISCUSSION

Drug - excipients compatibility study

The thermo grams of Flurbiprofen and mixture of excipients with drug was obtained as given in figure1 and 2. The melting point of Flurbiprofen is 110ºC-115ºC. The peak of Flurbiprofen was found at 115.84 ºC as shown in figure-1 a) and. The DSC spectra of drug and excipients in physical mixture showed peak at 116.43 ºC in figure-1 b). The availability of same peaks in both spectra confirmed the physicochemical stability of drug with the excipients used in the study.

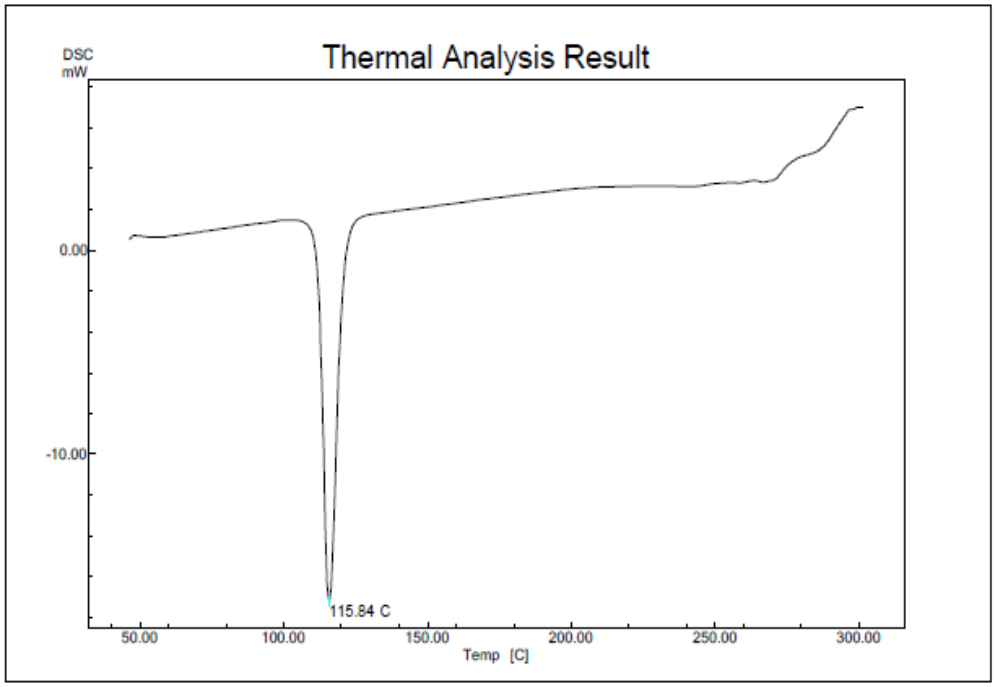


Figure1- a) : DSC study of Drug

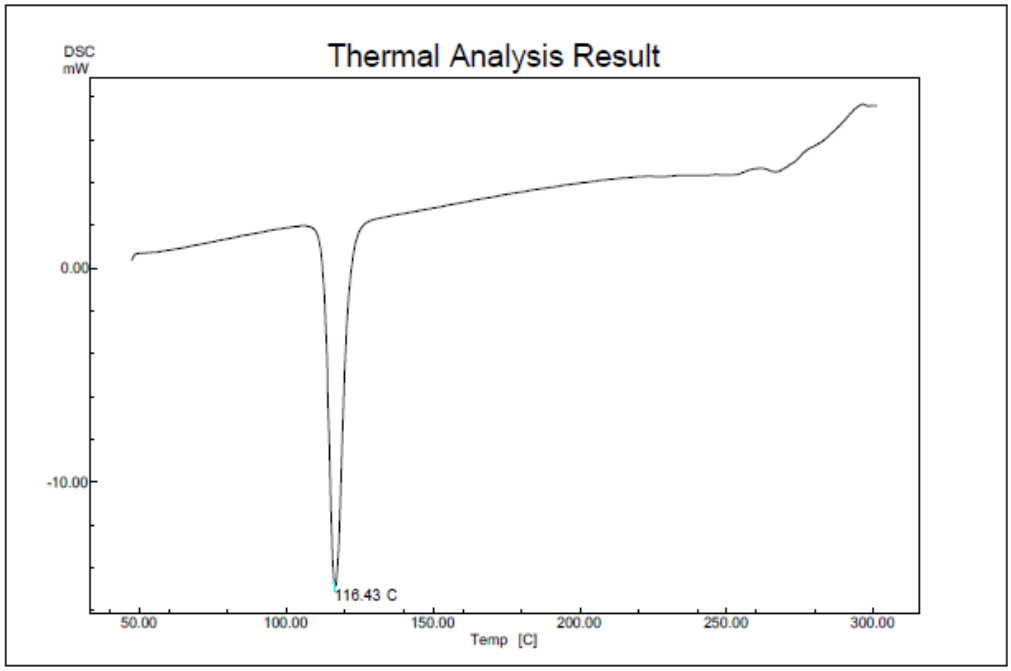


Figure1-b): DSC study of Drug and excipients

Effect of different extruder screen size on pellets

At 0.87 mm extruder screen size all spheroids got hard and formation of fines occurred during spheronization step. At 0.50 mm extruder screen size all spheroids got uniform particle size range and highest amount of % yield i.e. 75% was obtained as shown in figure-2.

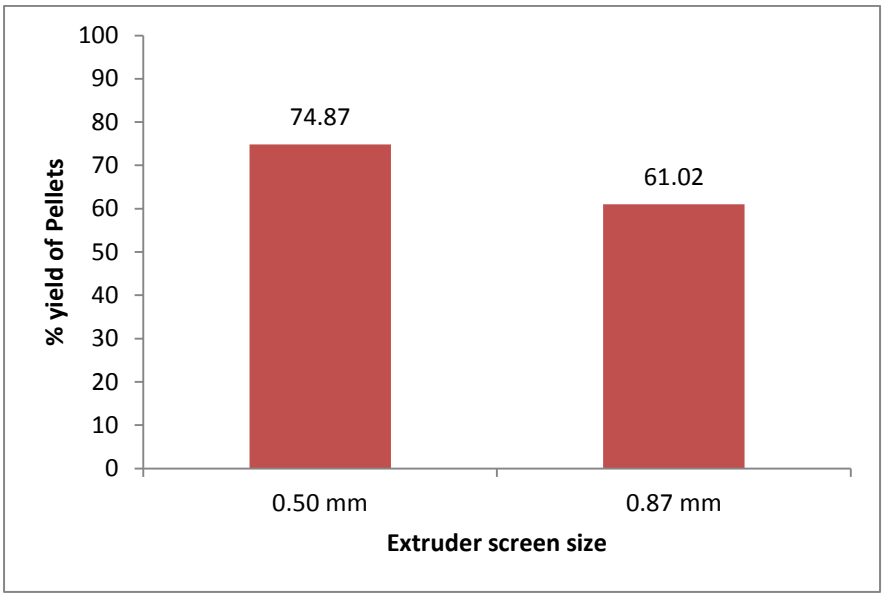


Figure2: Effect of different extruder screen size on pellets

Effect of different %LOD of extrudes on pellets

At 25% LOD all extrudes got hard and formation of fines occurred during spheronization step. At 20% LOD highest amount of % yield i.e. 75% was obtained. At 10 % LOD of the pellets the particle size is uniform in all the selected size range of the study; the usable yield was only 47%. While increased LOD up to 15% and 20% yield of pellets increased 61% and 75% respectively as shown in figure3. The narrowing of the pellet size distribution failed to happen at lower %LOD because the moisture present in extrudes was squeezed out on the surface of spheroids during the spheronization step and liquid bridge formation occur between two newly formed pellets and pellets get agglomerated, resulting in formation of larger size pellet (Otsuka M et al. 1994). All batches have angle of repose value in an excellent flow property range of 20.22 to 29.74.

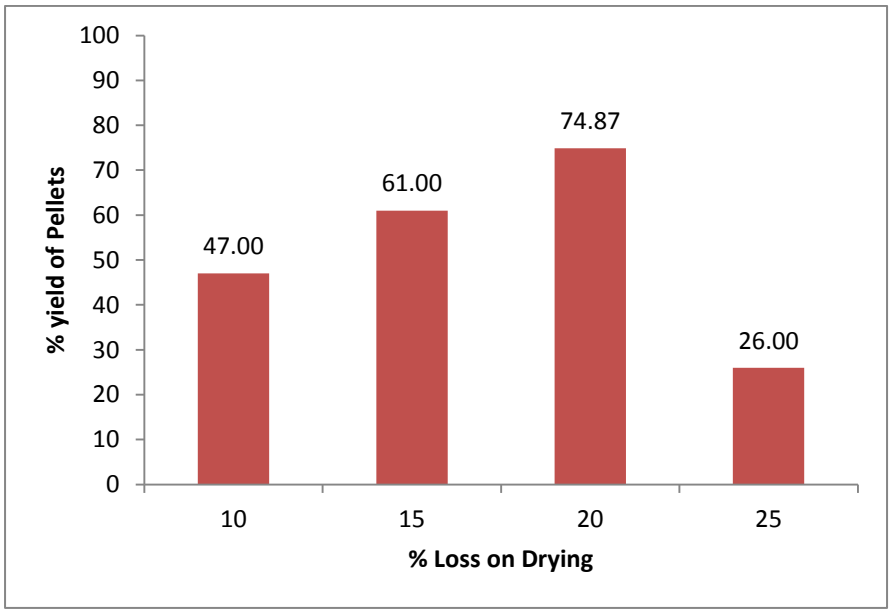


Figure 3: Effect of different %LOD of extrudes on pellets

Effect of Spheronization time on pellets

At 420 seconds pellets obtained for all selected size range was similar in weight. At 180 and 300 second spheronization time, % yield obtained in the pellets size range gradually increased; i.e. 49% and 79%. At lower time period; i.e. 120 seconds proper size distributed pellets yield was not obtained in size range as shown in figure-4. This occurred due to less time available to gain proper spherical shape from extrudes. During longer time for spheronization high attrition force applied on spheroids and reduced size pellets were obtained (Alvarez L et al. 2004)[12]. All batches gave angle of repose value in a good flow property range of 20.34 to 34.56.

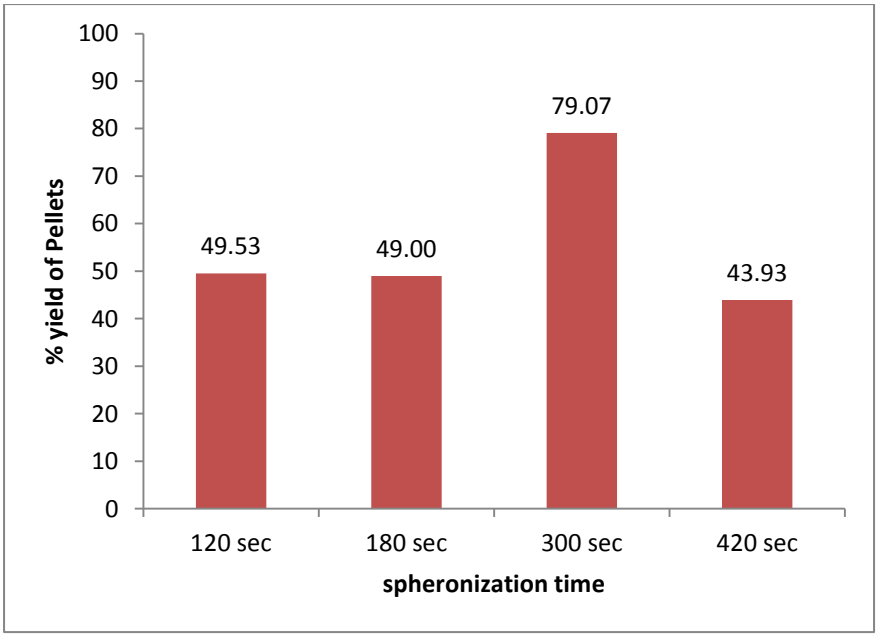


Figure 4: Effect of Spheronization time on pellets

Effect of Spheronization speed on pellets

At 1200 rpm pellets obtained in the usable size range was highest; i.e. 73.67% compared to that of 600 rpm and 1500 rpm. At 300 rpm and 600 rpm pellets obtained were not uniformly size distributed and at this speed pellets in yield size range was only 48% and 43% respectively as shown in figure-5. At 1500 rpm pellets obtained in selected size range was 42.5%. All batches have angle of repose value in a good flow property range of 22.54 to 32.21.

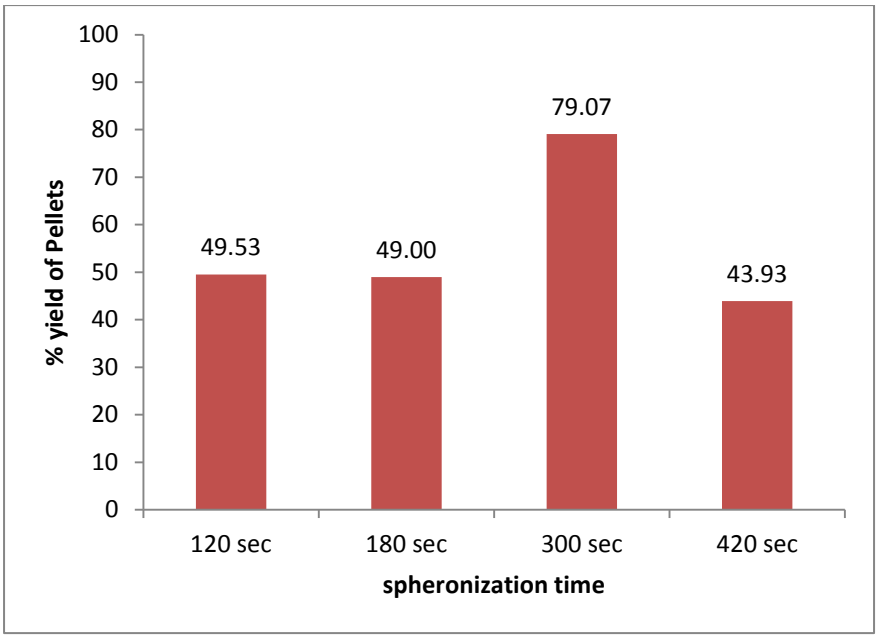


Figure-5: Effect of Spheronization speed on pellets

Characterization of Flurbiprofen coated pellets

The % yield of all batches ranged from 74 % to 81%. The highest % yield of 80.67% was obtained in batch FT4. All batches show value of yield above 70%; means the method selected for pelletization was reliable. This study helped in the ease to know the requirement of change in process parameters and effect of the formulation parameters.

The drug content of all nine batches was in the range of 96.67% to 97.73%w/w. Thus, all nine batches show almost similar drug content. Higher percentage drug loading is the main advantage of extrusion spheronization technique, among the other methods of pelletization. The drug content of all nine batches also shows good reproducibility.

The data of angle of repose varied from 22.87 to 27.84 for all the batches, which is in the acceptable range. The highest value of angle of repose was obtained for batch FT4.

The hardness value of all nine batches varied in the range of 5.07 kg/cm^2 to 7.30 kg/cm^2 which are in the desirable range of hardness for sustain release formulation. The harness value for FT4 batch

was 5.27 kg/cm^2. The hardness range was narrow; means it was not much more varied as per binder concentration.

The particle size of FT4 batch was 325.9 µm, this particle size would prove to be the desired one with respect to the pellets production. Smooth surfaced pellets were produced by using the extrusion spheronization.

In vitro dissolution study

Batch FT4 shows more drug release profile comparable to the theoretical drug release profile. The Q3 value of all batches varied from 20.59% to 34.99%. The Q3 value of theoretical profile was 30.00%, Q3 value of batches FT4 and FT8 were 29.24% and 29.00% respectively, which is close to our requirement as shown in figure6. The Q12 value of all batches varied from 57.56% to 61.91%. The Q12 value of theoretical profile was 59.97% which was closer in FT4 batch; i.e. 61.67%. The Q24 value of all batches varied from 90.86% to 96.43%. The Q24 value of theoretical profile was 96.43% which was more similar in FT4 batch.

The calculated values of n are more than 0.89 in Korsmeyer Peppas model; means it follows super case II transport type of diffusion. Most of R^2 values were nearer to 0.9783 in Higuchi model means they follow Higuchi model of dissolution kinetic models. Release mechanism from polymer follows Higuchi up to certain extent.

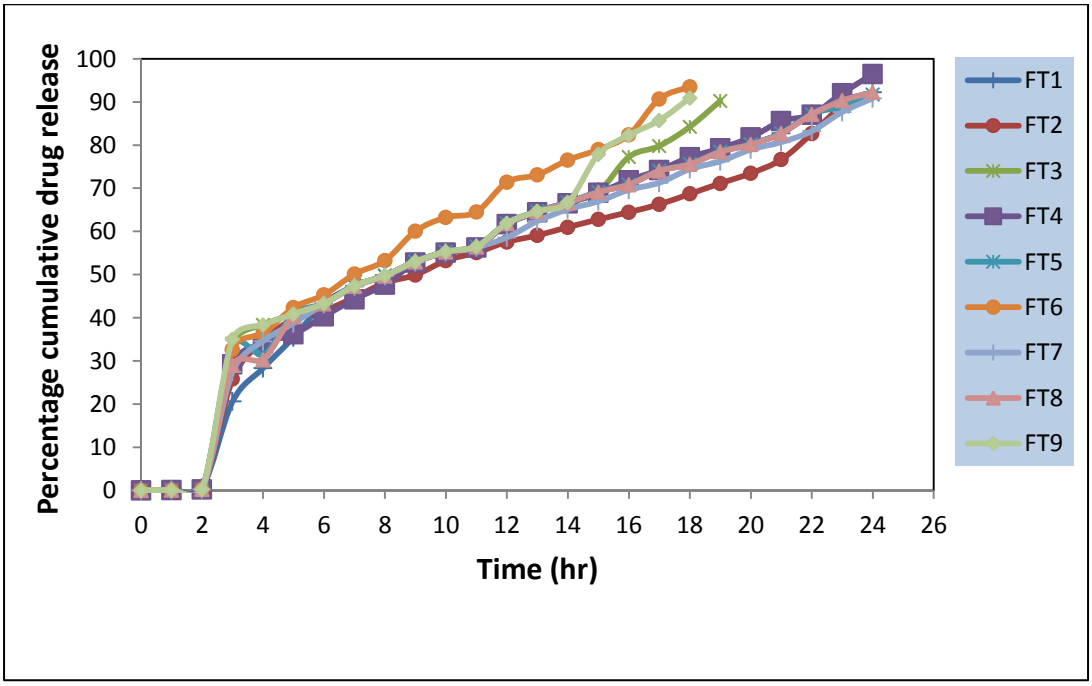
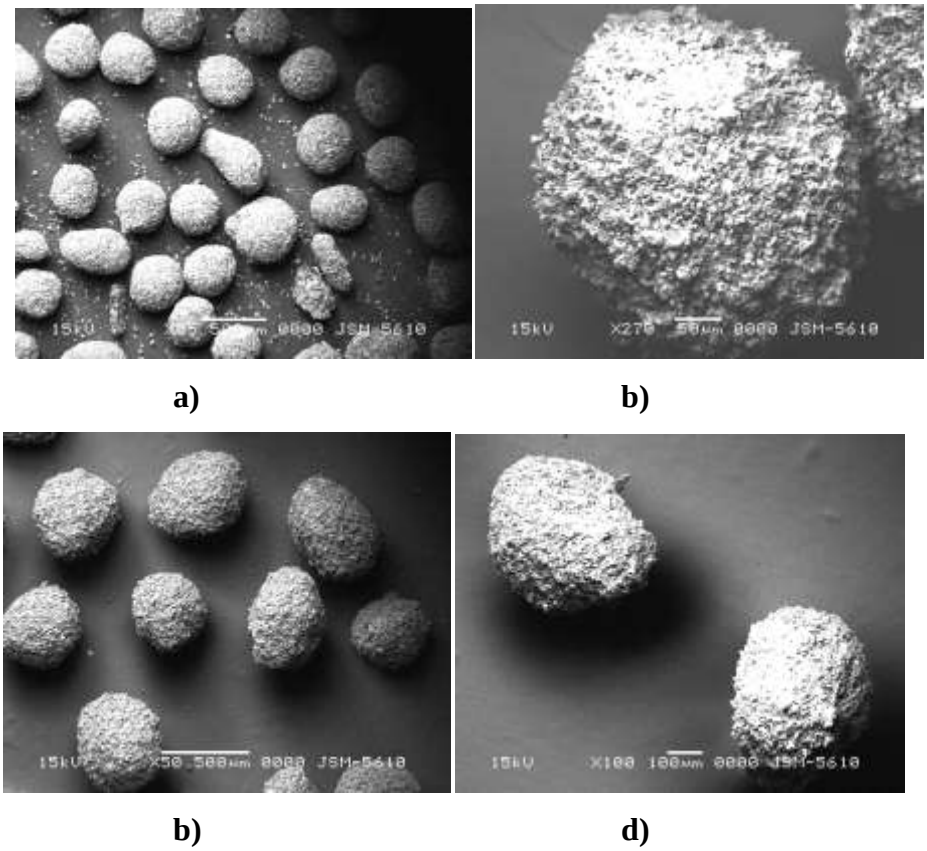


Figure 6: Comparison of dissolution profile of batch FT1 to FT9

Morphological analysis by scanning electron microscopy (SEM)

Scanning electron micrographs of Flurbiprofen core pellets of formulation FT4 are shown in figure-7 a), b), c) and d) respectively. The prepared pellets of batch FT4 appear almost spherical and intact in shape with smoother surfaces.



a) **b)**

b) **d)**

Figure-7: a), b), c), d): Scanning electron microscope image of Flurbiprofen coated pellets

Stability Studies

Results of stability study in table-3 reveal that the formulation remains stable over a period of 1 month at 40 ^{0}C / 75%RH conditions. As shown in result, there is no significant change in the assay of the formulation indicating the chemical stability of the formulation. The formulation was physically stable as evidenced by the visual observation.

CONCLUSION

An Enteric coated sustain release pellets were successfully developed by coating the Flurbiprofen core pellets with Eudragit RL100 and Eudragit RS100 which produces a 2 hr lag time in acidic medium followed by sustained release phase for 24 hrs. The produced coated pellets were stable for a period of 1 month when stored as per ICH guidelines. Therefore, these findings suggest the suitability of these polymers for preparing the above mentioned formulation. Hence, it can be concluded that the enteric coated sustain release pellets would be a promising drug delivery system for systemic administration of Flurbiprofen for rheumatoid arthritis.

ACKNOWLEDGEMENT:

Authors are thankful to all management members of Shree S.K. Patel College of Pharmaceutical Education and Research, a constituent institute of Ganpat University, Gujarat for providing the necessary facility to carry out this research work.

REFERENCES

1. Erkoboni, DF. Extrusion-spheronization as a granulation technique; In, Parikh DM (ed). Handbook of Pharmaceutical Granulation Technology. Marcel Dekker Inc, NewYork, 2010, 281-360.
2. Dukić-Ott, A, Thommes, M, Remon, JP, Kleinebudde,P ,Vervaet, C. Production of pellets via extrusion-spheronization without the incorporation of microcrystalline cellulose: a critical review. Eur J Pharm Biopharm 2009;71: 38-46.
3. Erkoboni, KA. Extrusion/spheronization. In, Ghebre-Sellassie I, Martin C (ed). Pharmaceutical Extrusion Technology. Marcel Dekker Inc, New York, 2003: 277-322.
4. ZimmK.R., Schwartz, J.B., O'Connor. Drug release from a multiparticulate pellet system. Pharm. Dev. Technol 1996; (1): 37–42.
5. Gandhi R. Using extrusion-spheronization to develop controlled-release formulations of azithromycin. Pharmaceutical Techno. 2005; 29(2):68-86.
6. Baert, J., Remon, J. Influence of amount of granulation liquid on the drug release rate from pellets made by extrusion spheronization. Int J Pharm 1993; 95: 135- 141.
7. Elbers, J, Bakkenes, H, Fokkens, J. Effect of amount and composition of granulation liquid on mixing, extrusion and spheronization. Drug Dev. Ind. Pharm 1992;18: 501-517.
8. Heng, P., Koo, O. M. Y. A study of the effects of the physical characteristics of microcrystalline cellulose on performance in extrusion spheronization. Pharm. Res. 2001; 18:480-487.
9. Rowe, R.C., York, P., Colbourn, E.A., Roskilly, S.J. The influence of pellet shape, size and distribution on capsule filling - a preliminary evaluation of three dimensional computer simulations using a Monte-Carlo technique. Int. J. Pharm. 2005;300: 32–37.
10. Sousa, J. J., Sousa, A., Podczeck, F., Newton, J. M. Influence of process conditions on drug release from pellets. Int. J. Pharm. 1996; 144: 159-169.
11. Ghebre-Sellassie, I. Pellets: A general overview. In, Ghebre-Sellassie I (ed). Pharmaceutical Pelletization Technology. Marcel Dekker Inc, New York, 1989:1-13.

12. Alvarez, L, Concheiro, A, Gomez-Amoza, JL, Souto, C, Martinez-Pacheco, R. Effect of microcrystalline cellulose grade and process variables on pellets prepared by extrusion-spheronization. Drug Dev. Ind. Pharm. 2002; 28:451-456.