

FORMULATION AND EVALUATION OF FLURBIPROFEN SOLID DISPERSION

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ABSTRACT

Objective: The present investigation is concerned with the formulation and evaluation of Flurbiprofen solid dispersion and microsphere for prolonging the duration of action of the drug.

Method: Flurbiprofen dose is prepared as a capsule containing two types of units; the first one is the fast release unit prepared as a solid dispersion that gives the loading dose for instant pain managements and the other is the controlled release unit which is prepared as microspheres to maintain drug-plasma concentration within the therapeutic level for 24 hours. Microspheres were prepared by solvent evaporation method using ethyl cellulose and different types of Eudragit polymers. The effect of the type and the concentration of polymer, temperature, pH of the continuous phase and the stirring speed were studied, also the release profile, the entrapment efficiency and the particle size were also analyzed to select the best microsphere formula.

Results: Microsphere Formula R14 was selected as the best selected formula due to its high entrapment efficiency, high drug loading concentration and its good release profile. A hard gelatin capsule containing Flurbiprofen equivalents to 100mg of fast release dose and 100 mg of controlled release unit was prepared, a further investigation about capsule quality control.

Conclusion: The overall results suggested that a solid dispersion and microspheres of flurbiprofen capsule with a better biopharmaceutical properties and prolonged duration with fast onset of action could be obtained.

Keywords: Surface solid dispersion, Flurbiprofen, Microspheres, Ethyl cellulose, Eudragit RS100, Eudragit L100, Hydrophobic drugs, and Sodium starch glycolate.

INTRODUCTION

Solid dispersion is a product that consists of two or more different components, usually a hydrophilic carrier and a hydrophobic drug in a solid state, prepared by melting dissolution in solvent or melting solvent method. Solid dispersion is a good method for enhancing bioavailability of poor water-soluble drugs. When the solid dispersion is exposed to aqueous media, the carrier dissolves and the drug releases as fine colloidal particles leading to increase both solubility and bioavailability for drug [1].

Solid dispersion formula of flurbiprofen with PVP, PEG 600 and Sodium starch glycolate were used to provide a fast initial loading dose [2]. Also solid dispersion may reduce gastric irritation associated with flurbiprofen [3], solid dispersion can increase or decrease the release depending on polymers used. Ethyl cellulose preparation can produce a prolonged release duration while Sodium starch glycolate can reduce the release time. Poor water soluble drug class II has a delayed absorption from the gastrointestinal tract so the solubility is the rate-limiting step for absorption.

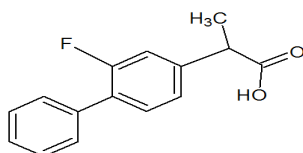


Fig. 1: Chemical Structure of Flurbiprofen

Flurbiprofen is a non-steroidal anti-inflammatory drug used to treat the inflammation and pain of arthritis [4, 5].

MATERIALS AND METHODS

Materials

Flurbiprofen, FDC limited-INDIA, Ethyl cellulose, Carboxy methyl cellulose (S.D.I -IRAQ), HCl and chloroform (BDH Chemical LTD-England), Eudragit RS100 (Provizer pharma-India), Eudragit L100 (SDI-IRAQ), Sodium starch glycolate and PEG 6000(Provizer

pharma-India), Polyvinyl pyrrolidone (PVP) Riedel De Haen AG Seelze, Hannover, Germany.

Methods

Determination of the Melting Point

Determination of flurbiprofen melting point was done according to the USP pharmacopeia using a capillary tube with close end filled with flurbiprofen to measure the melting point using an electrical melting point apparatus, where the melting point was recorded [6].

Determination of the λ_{\max}

Twenty five milligrams of flurbiprofen was dissolved in a 100 mL methanol to prepare a 0.25 mg/mL stock solution. From this stock solution, 4mL were transferred to 100mL volumetric flask and diluted with phosphate buffer solution of 7.4 pH, then scanned by the UV spectrophotometer at the range of 200- 400 nm, in order to determine the wave length of the maximum absorbance (λ_{\max}) of flurbiprofen. The same steps were repeated with 0.1 N hydrochloric acid (pH 1.2) and methanol to obtain the λ_{\max} of flurbiprofen in each of those medias [7].

Preparation of the Calibration Curves

Calibration curves of flurbiprofen in 0.1 N HCl (pH 1.2) and phosphate buffer USP (pH 7.4) were constructed by preparing dilution series of the drug from 0.25 mg/ml in methanol flurbiprofen stock solution. The prepared samples were analyzed spectrophotometrically at λ_{\max} of 247nm for 0.1 N HCl (pH 1.2), and phosphate buffer (pH 6.8). The absorbencies obtained were recorded [7].

Flurbiprofen Microsphere Preparation

Microspheres were prepared by the emulsion solvent evaporation method. Calculated quantity of flurbiprofen was dissolved in 25ml of chloroform to form a homogenous polymer solution. Then a measured amount of the polymer was added to the chloroform and mixed thoroughly. The resulting mixture was then added as a drop by drop using a burette to 1000ml of 0.01N HCl solution containing

sodium carboxymethyl cellulose (0.25 w/v %) and 1 % (v/v) tween80 while stirring at 1000 rpm speed, then oil in water emulsion was formed. Continuous stirring was done at room temperature for 1 hour to produce spherical microspheres and ensures that all the chloroform were removed completely. The microspheres were collected by vacuum over Buchner funnel and fitted with a filter paper and washed repeatedly with distilled water to get pure microspheres, then dried in 40°C for 24 hours, a spherical microspheres were formed [8, 9].

By varying the polymer used, the stirring speed, the temperature, and the pH of continuous phase, many formulas were prepared by this method as shown in table 1. Formulas A1, A2, A3 used to investigate the effect of varying drug: ethyl cellulose ratio, both of

polymer and flurbiprofen are dissolved in 25ml chloroform and added as a drop wise in 100ml aqueous 0.01N HCl solution containing 0.25%(W/V) carboxy methyl cellulose and 1%(W/V) Tween 80 with the stirring speed maintained at 1000rpm. Formulas L4,L5,L7,L8,R9 and R10 used to investigate the effects of varying Eudragit L100 concentration and ethyl cellulose while formulas (R9-R14) investigate the effect of varying the concentration of ethyl cellulose, Eudragit L100 and Eudragit RS100.

Modifications of pH of aqueous phase, stirring speed are done to the formula containing ethylcellulose and eudragit RS100 formulas (R9-R14) while the effect of lowering temperature from 25°C to 4°C is studied on the selected formula R14 as shown in tables 1, and 2.

Table 1: Different formulas of microsphere can be prepared by emulsion solvent evaporation method

Formula	Flurbiprofen	Ethyl cellulose	Eudragit L100	Eudragit RS100
A1	1	1	-	-
A2	1	2	-	-
A3	1	3	-	-
L4	1	0	2	-
L5	1	0	1	-
L6	1	1	1	-
L7	1	1	2	-
L8	1	2	1	-
R9	1	1	0.5	0.5
R10	1	-	-	1
R11	1	-	-	2
R12	1	0.5	-	1.5
R13	1	1	-	1
R14	1	1.5	-	0.5

Table 2: Investigate the effect of pH, stirring speed, and temperature on formulas

Formula	Flurbiprofen	Ethyl cellulose	Eudragit RS100	Modification
R15	1	-	2	Using 0.1 HCl in preparation of continuous phase
R16	1	0.5	1.5	
R17	1	1	1	
R18	1	1.5	0.5	
R19	1	-	2	Changing stirring speed to 2000 RPM
R20	1	0.5	1.5	
R21	1	1	1	
R23	1	1.5	0.5	
R14	1	1.5	0.5	temperature of continuous phase around 25°C
R28	1	1.5	0.5	temperature of continuous phase around 4°C

Evaluation of the Prepared Microspheres

1- Percent Yield

The percentage of the production yield was calculated from the weight of the dried Microspheres (W1) and the sum of initial dry weight of the starting materials (w2) as the following equation [10].

$$\% \text{ Production Yield} = W1 / W2 \times 100\%$$

2- Drug Content.

To determine the drug content of the prepared microspheres, around 25 mg sample of each prepared formula was placed in a 50ml volumetric flask add methanol then the sample was sonicated for 1 hour to ensure complete destruction of microsphere and all flurbiprofen is released after that the sample is filtered using 0.45 µm micro-filter, 2ml of the filtrate was transferred to a 50ml volumetric flask were the volume completed using 7.4 phosphate buffer (USP) and the absorbance measured using UV-Visible spectrophotometer at 247 nm. The amount of drug inside the microsphere was determined using the calibration curve [11].

3- Entrapment Efficiency [12].

$$\% \text{ Entrapment Efficiency (EE)} = \frac{\text{Actual Drug Content}}{\text{Theoretical Drug Content}} \times 100\%$$

Dissolution Test

Dissolution studies of flurbiprofen microsphere were performed in a USP dissolution apparatus I (basket). Capsule filled with microsphere (equivalent to 100 mg flurbiprofen) were placed in 900 mL of dissolution media 0.1N HCl for 2 Hrs. then the media was replaced by same amount of phosphate buffer USP (7.4) at 37°C ± 0.5 and rotated at 75 rpm [13, 14].

5 mL of samples were withdrawn for analysis periodically and replaced by the same volume of fresh media maintained at 37°C ± 0.5. The withdrawn samples were filtered with a millipore filter (pore size 0.45 µm). The amount of flurbiprofen released in the medium was determined spectrophotometrically at λ_{max} of 274 nm. The amount of flurbiprofen released at different time intervals was determined using the equation obtained from the calibration curve at the same PH of dissolution media finally the percent of drug release was plotted against time to obtain dissolution profiles [15].

Preparation of Fast Release Units

Flurbiprofen fast release units can be prepared as a surface solid dispersion using co-grinding method as shown in table 3: It involves the preparation of physical mixture of flurbiprofen with minimum amount of methanol and SSG as a water-insoluble carrier using

mortal and pistol after that the mixture is sieved using 50 mesh sieve and dried in oven for 2 hours [16].

Table3: Fast release units formulas

Formula	Flurbiprofen	SSG	Drug: SSG Ratio
F1	5	5	1:1
F2	5	10	1:2
F3	5	15	1:3

Evaluation of Fast Release Layer

Drug Content Analysis

Drug equivalent to 20mg of flurbiprofen is transferred to a 50 ml volumetric flask filled with 7.4 phosphate buffer then the absorbance was measured at 247 nm. The drug content was calculated using calibration curve at 7.4 phosphate buffer.

Dissolution Study

Capsule containing 200mg of formula F1 was subjected to dissolution test at the same condition used in microsphere test.

Final Formula

Mixing amount from the selected formula F1 of fast release particles and controlled release microsphere (R14) equivalent to 100mg of flurbiprofen as and fill it in hard gelatin capsule(size 00) as shown in table 4.

Table 4: Final formula

Final Formula	Amount of Formula equivalent 100mg 1capsule	Batch Formulation 40 capsules
Fast release granules	200mg	8gm
Controlled release microsphere	0.328gm	13.12gm
Total weight	528mg	21.12gm

Evaluation of Final Formula

Flow Properties

For the final mixture powder flow properties was determined in terms of angle of repose, the powder were poured through the walls of a funnel, which was fixed at a position such that its lower tip was at a height of exactly 2.0 cm above hard surface. The microspheres were poured till the time when upper tip of the pile surface touched the lower tip of the funnel. The \tan^{-1} of the height of the pile /radius of its base gave the angle of repose angle of repose is an indicator of powder flow properties as show in table 5 [17].

$$\tan \theta = \text{height} / \text{radius}$$

Table 5: Angle of repose and flow properties

Flow properties	Angle Of Repose
Excellent	25-30
Good	31-35
Fair(aid not needed)	36-40
Passable(may hang up)	41-45
Poor(Must agitate vibrate)	46-55
Very poor	56-65
Very-very poor	≥66

Disintegration Time of Capsule

The disintegration time of the prepared capsule was measured using the disintegration apparatus and method as described in the USP. A

capsule was placed over the mesh of the disintegration apparatus tube which was immersed in 900 mL beaker containing a disintegration media of 0.1 N HCl held at $37^{\circ}\pm 2^{\circ}\text{C}$ The length of the time needed for the capsules to break down into its original beads was recorded as the time of disintegration [6].

Content Uniformity

To ensure consistency of dosage units, each capsule in the batch should have drug substance content within a narrow range around the label claimed (200) mg of flurbiprofen. A whole capsule is open in 100 ml volumetric flask filled with 50ml methanol, then sonicated for 1hr after that the sample is filter and 5 ml of filtrate is transferred to 100ml volumetric flask complete the volume with 7.4 phosphate buffer USP with hand shaking then 10 ml of diluents is transferred to 100 ml volumetric flask after that the volume completed to 100 ml with phosphate buffer ,the absorbance measured using UV-Visible spectrophotometer at 247 nm The amount of drug inside the capsule was determined using the calibration curve.

Scanning Electron Microscopy and Light microscopy

Scanning Electron Microscopy (SEM) is an electron optical imaging technique that elemental information. Scanning Electron Microscopy is useful for characterizing the size and the morphology of microscopic specimens. Scanning Electron Microscopy analysis requires a small amount i.e., 1-10 to 10-12 mg of a solid specimen that is coated with a conductive substance to inhibit the sample charging. The sample is placed in an evacuated chamber and scanned in a controlled pattern by an electron beam. Interaction of the electron beam with the specimen produces a variety of physical phenomena that is detected to form mages and provide elemental information about the sample, on other hand light microscope can give information only about shape and size of microsphere [18, 19].

RESULTS AND DISCUSSION

Characterization of Flurbiprofen

Determination of Melting Point

The melting point of flurbiprofen was found to be 117°C This is similar to what's reported by the United State pharmacopeia.

Determination of λ_{max}

Maximum wave length absorbance (λ_{max}) for diluted (0.01 mg/mL) solution of flurbiprofen in (0.1 HCl, phosphate buffer 7.4, and methanol was 247nm i.e. there was no shifting in the λ_{max} upon changing the pH or changing solvent to methanol. The obtained results are in agreement with the reference [20]. The reading is shown in figure 2.

Calibration Curves

Calibration curves of Flurbiprofen in 0.1 N HCl (pH 1.2 and phosphate buffer (pH 7.4) were constructed and are represented in figures 3and 4, respectively.

Controlled Release Microsphere:

A1-A3, yield percent, entrapment efficiency and drug content of microsphere are shown in table 6 that formulas A1, A2, A3 to investigate the effect of varying drug: ethyl cellulose ratio, increasing the ratio of ethyl cellulose will increase the yield and entrapment efficiency this may be a result of high viscosity and fast solidification of the dispersed phase contributed to reduce porosity of the microspheres, increase viscosity of solution, faster polymer precipitation on the surface of microspheres may delay drug diffusion leading to decrease drug diffusion to the continuous phase [21]. In ethyl cellulose formula the solubility of flurbiprofen in acid stage is greater than the saturation solubility this may be attribute to the use of surface active agent Tween 80 in the formulation of microsphere that increase drug solubility [22].

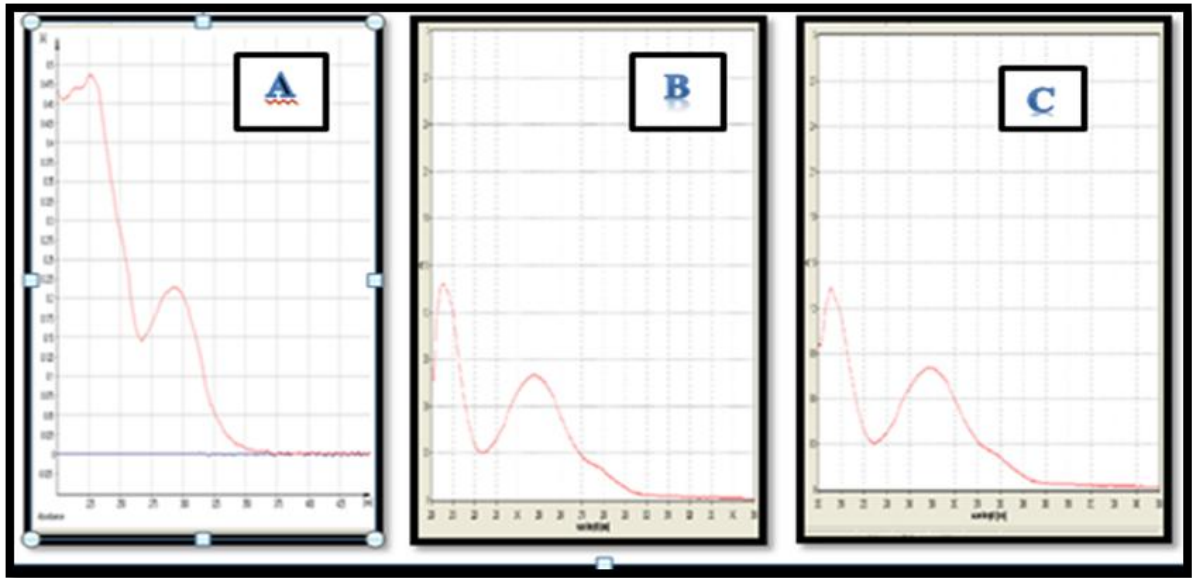


Fig. 2: The UV Spectrum of Flurbiprofen in Different Medias: (A: in Methanol, B: in 0.1N HCl, and C in Phosphate Buffer 7.4)

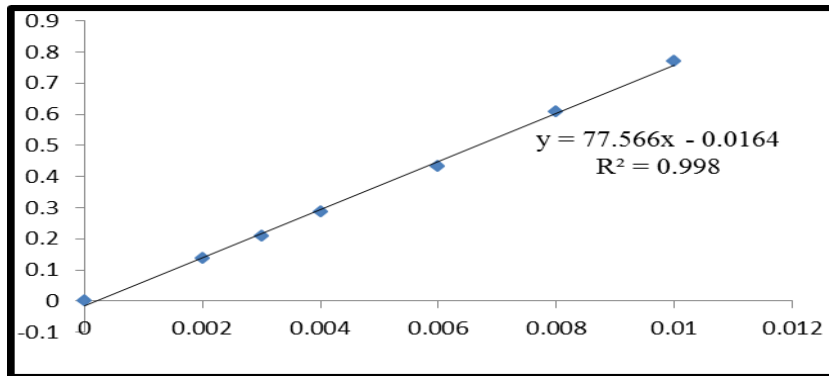


Fig. 3: Calibration Curve of Flurbiprofen in 0.1HCl (pH 1.2)

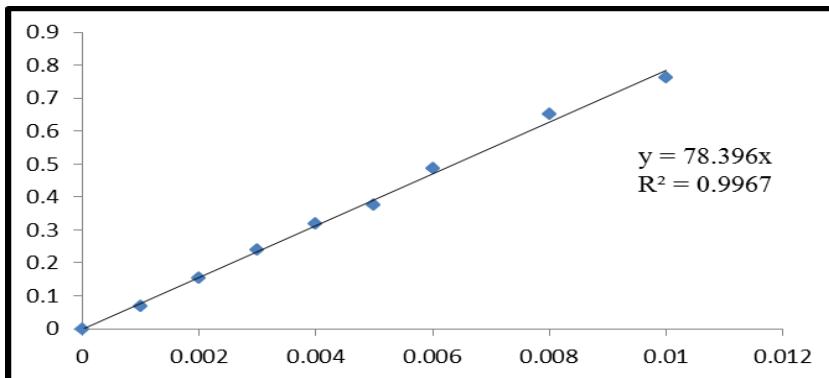


Fig. 4: Calibration Curve of Flurbiprofen in Phosphate Buffer pH 7.4

Table 6: Effect of Ethyl cellulose concentration on the entrapment efficiency

Formula	Yield Percent %	Sample weight mg	Drug content %	Entrapment efficiency %	100mg flurbiprofen in total dose in mg
A1	low weight	-	-	-	-
A2	55	25	9.69	15.99	1031
A3	53.5	25	8.67	18.21	1152

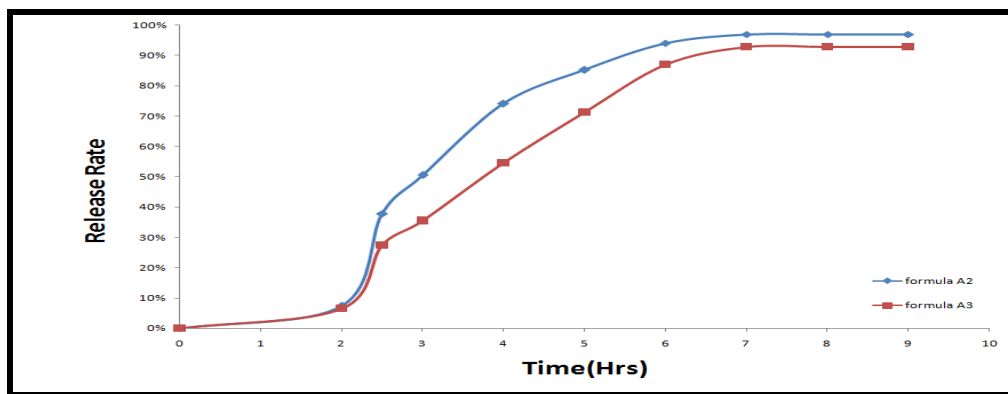


Fig. 5: The Effect of Ethyl Cellulose Concentration on the Release of Flurbiprofen Microsphere in Formulas A2, and A3

While in table 7 the Eudragit L100 was used in the preparation of microsphere to control the drug release [23]. Adding Eudragit L100 in various ratios with ethyl cellulose will increase drug content and entrapment efficiency the same result was reported in other study [24], this may be attributed to low solubility of Eudragit L100 in low pH media.

Eudragit L100 is dispersed uniformly in chloroform, explains the low yield in L5 formula because the drug and Eudragit L100 will

separate as soon as the solvent removed and the presence of ethyl cellulose on the other formula will prevent separation of Eudragit L100 and flurbiprofen.

While the release rate was inversely proportional with the amount of Eudragit L100 used to some extent, this may be attributed to the high solubility of Eudragit L100 in phosphate buffer with pH 7.4 , a lower flurbiprofen solubility in acid stage with microsphere with L100 attribute to pH dependent solubility of Eudragit L100 [25].

Table 7: Ethyl cellulose/Eudragit L100 ratio on entrapment efficiency

Formula	Yield Percent %	Sample weight mg	Drug content %	Entrapment efficiency %	100mg Flurbiprofen in total dose in mg
L4	47.33	25	21.55	30.61	463
L5	Low weight	-	-	-	-
L6	50.33	26.1	28.47	42.99	351
L7	42.25	25	25.89	43.76	386
L8	53	28.8	23.7	50.25	421

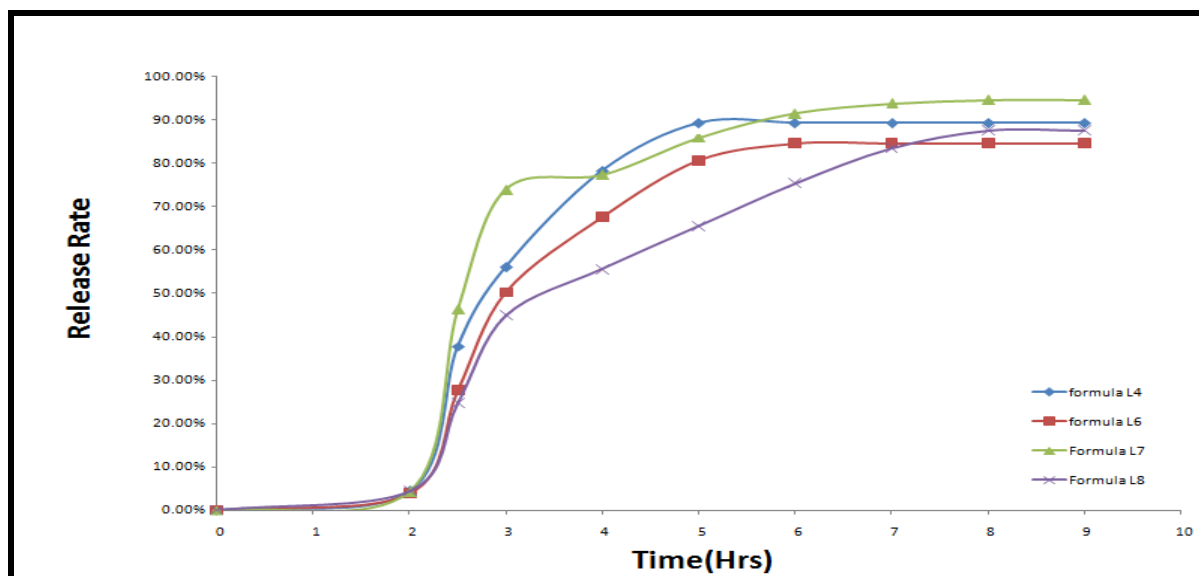


Fig. 6: Eudragit L100 Concentration on the Release of Flurbiprofen Microsphere in Formulas L4, L6, L7, and L8

On the other hand, table 8 showed a dramatic increase in the yield, drug content and entrapment efficiency by the combination of ethyl cellulose and Eudragit RS100 in different ratios which is due to the higher solubility of Eudragit RS100 than Eudragit L100 in organic phase, and low solubility of Eudragit RS100 in aqueous acid

compared to ethyl cellulose alone. Also the yield percent, drug content and entrapment efficiency are inversely proportion with the amount of Eudragit RS100 used. R10 formula has low yield and entrapment efficiency because of low solubility of Eudragit L100 in chloroform [26].

Table8: Ethyl cellulose, Eudragit L100 and Eudragit RS100 on entrapment efficiency

Formula	Yield Percent %	Sample weight mg	Drug content %	Entrapment efficiency %	100mg Flurbiprofen in total dose in mg
R9	53.33	33.2	16.95	27.12	589
R10	Low weight	-	-	-	-
R11	70.33	25.4	24.48	51.66	408
R12	85.33	20.1	32.20	82.45	310
R13	86.66	20.5	28.39	73.81	352
R14	90.33	21.4	30.46	82.56	328

Introducing Eudragit RS100 in the formula will prolong the release rate compared to formulas with Eudragit L100 and ethyl cellulose only as

shown in figure 7, therefore the release rate is inversely proportional with the ratios of Eudragit RS100 to other polymer used.

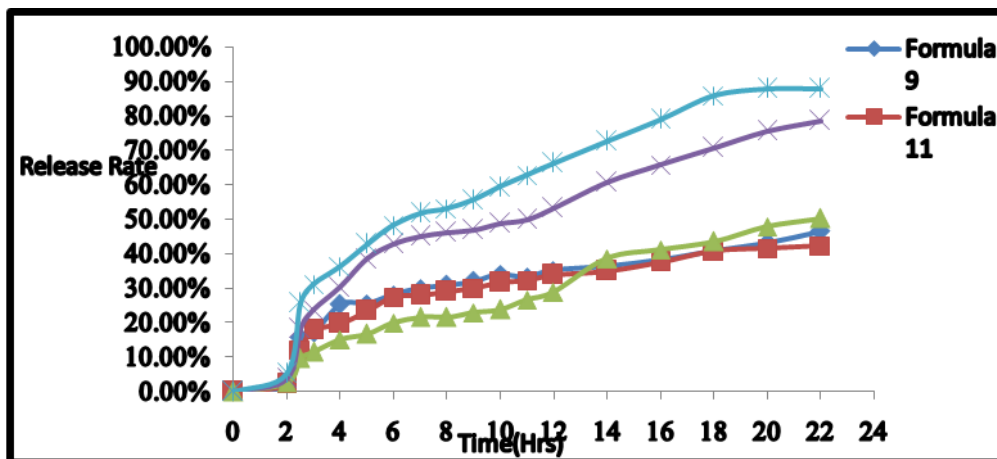


Fig. 7: Ethyl Cellulose, Eudragit L100 and Eudragit RS100 on Flurbiprofen Microsphere Release.

While using 0.1N HCl instead of 0.01N HCl lead to decrease the pH of aqueous phase from (2.4±0.2) to (1.15±0.2), resulting to decrease

the release rate, and a mild effect was seen on entrapment efficiency as shown table 9 and figure 8.

Table 9: The effect of pH of continuous phase on entrapment efficiency

Formula	Yield Percent %	Sample weight mg	Drug content %	Entrapment efficiency %	100mg Flurbiprofen in total dose in mg
R15	76.66	21.4	28.01	64.43	356
R16	88	23	26.76	70.65	373
R17	88.33	22.8	27.34	72.46	365
R18	92	23.1	28.71	79.25	348

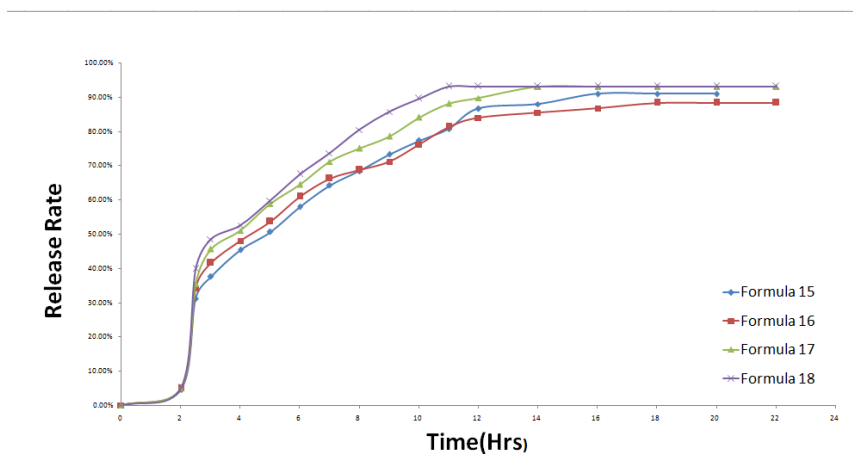


Fig. 8: Effect of Continuous Phase pH on Flurbiprofen Microsphere Release

On the other hand changing the stirring speed from 1000rpm to 2000 rpm will lead to decrease yield and entrapment efficiency, as

shown in table 10 this may due to reduction of particle size of emulsion droplet forming smaller microspheres.

Table 10: The effect of stirring speed on entrapment efficiency

Formula	Yield Percent %	Sample weight mg	Drug content %	Entrapment efficiency %	100mg Flurbiprofen in total dose in mg
R18	63.33	33.3	16.80	32.10	594
R19	55.00	25.2	22.52	37.16	443
R20	62.00	25	26.15	48.64	382
R21	55.10	25.3	27.79	45.94	359

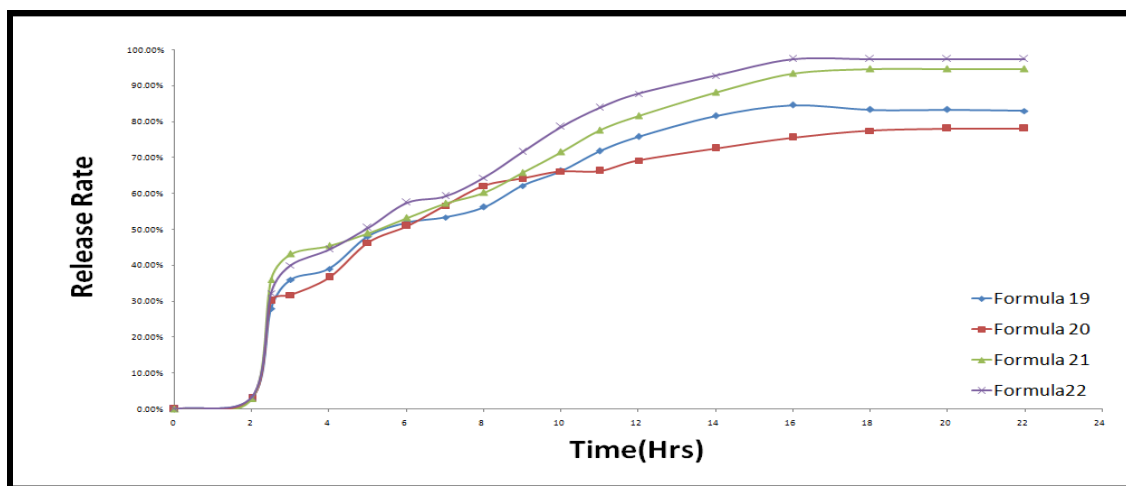


Fig. 9: Effect of the Stirring Speed on Flurbiprofen Microsphere Release

While lowering the temperature of the continuous phase up to 5°C instead of 25°C will lead to the production of very fine homogenous

in size microsphere with a high release rate, as shown in table 11, whoever the yield is dramatically reduced as shown in figure 10.

Table 11: The effect of temperature on the entrapment efficiency

Formula	Yield Percent %	Temperature	Sample weight	Drug content	Entrapment efficiency %
R14	90.3	25°C	0.428	31.89	72.99%
R23	55	5°C	0.378	29.98	49.47%

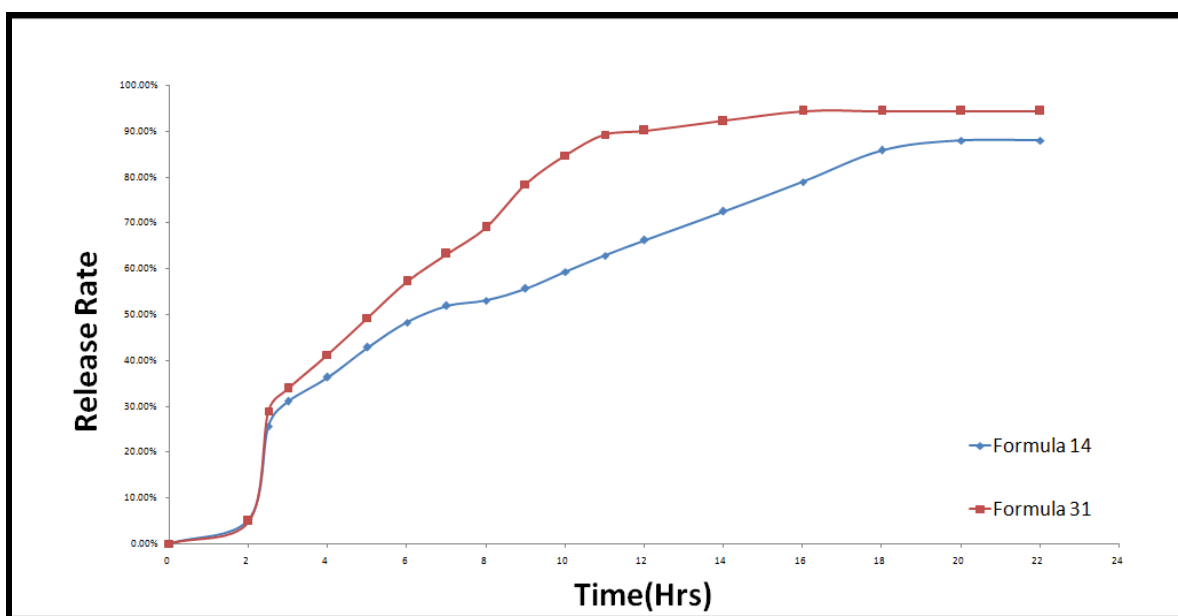


Fig. 10: The effect of temperature on Flurbiprofen microsphere release rate

Fast Release Unit

Drug Content Analysis

For all 3 formulas, a uniform drug distribution with carrier ranging from 96.1% to 103.4%

A semi-solid state was formed in formula F1 while tacky powder was formed in F2 formula and free flowing powder was formed in F3 indicate increase in the melting point with increase amount of PEG 6000.

Characterization of R14

Angle of repose was measured for the final formula powder 33.69, the mixture has good flow properties according to table 4, and there is no need to any lubricant to enhance the flow. Good flow properties may be attributed to the shape of microsphere (spherical) same result is found in Curcumin microsphere [27].

Also, the disintegration time ranging from (3.5 to 5.25) minutes which is within the limits (not more than 15 minutes), while the release profile for flurbiprofen capsule of final formula compared to the ordinary commercial 100 mg flurbiprofen tablet (Maximus®) is shown in figure 11.

Low release rate is shown in the acid stage, this may be due to low solubility of flurbiprofen in low pH medium, in buffer stage, the release was too fast at the first hour from phosphate buffer dissolution providing the loading dose and controlled release with slow release for the rest time of dissolution, while ordinary maximus tablet show no control release profile. Similar result was shown in flurbiprofen bilayer tablet [28].

Scanning electron microscope and light microscope

Scanning electron microscope shows smooth non-porous surface spherical microspheres same results were observed in a similar preparation method [29, 30, 31].

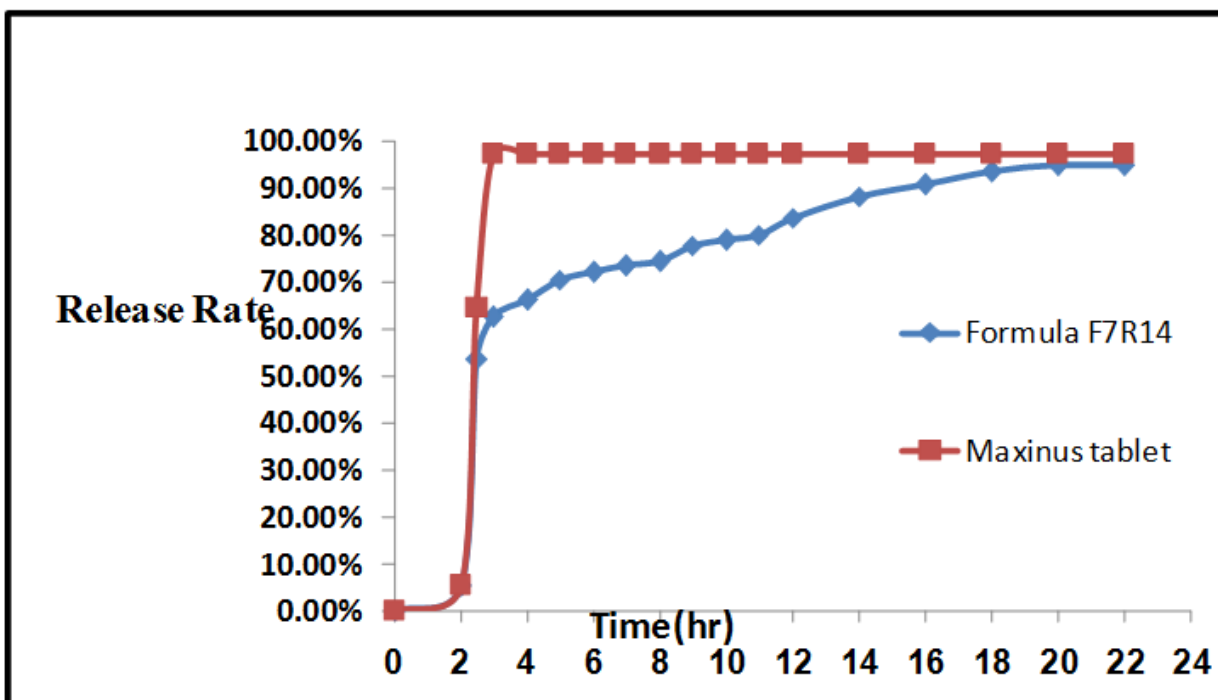
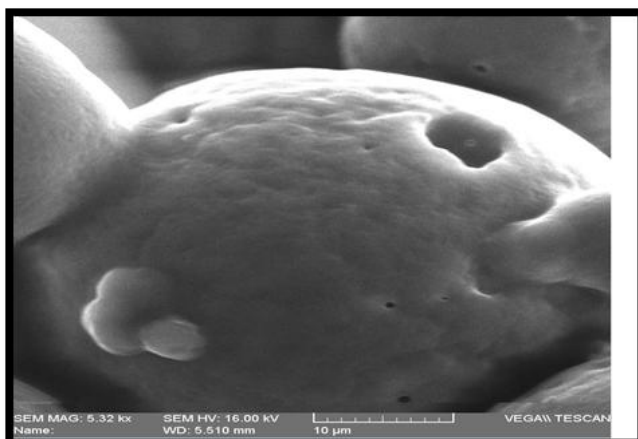
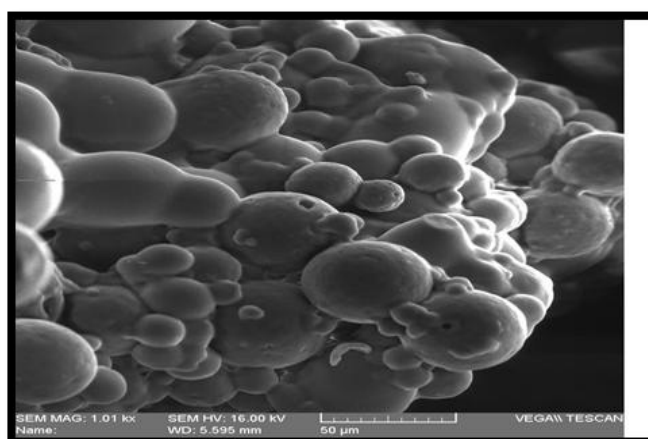


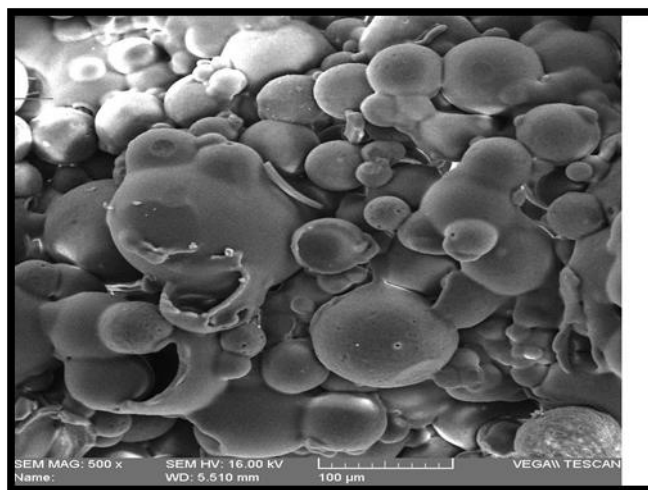
Fig. 11: Final capsule (Selected R14 Microsphere + Fast Release Unit) and Maximus®



A.



B.



C.

Fig. 12: A, B and C SEM photo in different magnification power

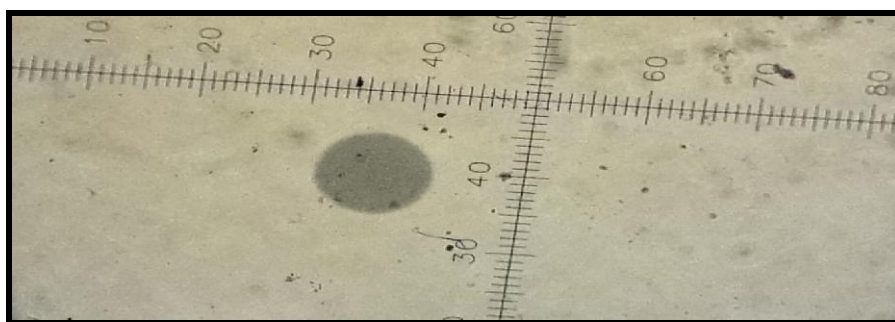


Fig. 13: Electron Microscope Photo for Formula R14

CONCLUSION

The overall results suggest that the release rate of flurbiprofen could be controlled to optimize patient need as a single dose by solid dispersion and microsphere techniques utilizing different variables to optimize best selected formula with modified release of the drug.

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