Formulation & Evaluation of Ciprofloxacin Controlled Release Floating Capsules

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ABSTRACT

Capsules are solid preparations in which the drug substances and/or excipients are enclosed in either a soft or hard soluble shell. The shell is normally made of gelatin or suitable polymeric material and results in a simple, tasteless, odourless, elegant, easy to swallow dosage form without the need for a secondary coating step. Controlled release dosage forms have attracted considerable interests as a mean of improving the dissolution rate & hence possibly bioavailability range of hydrophobic drugs. The poor solubility of ciprofloxacin leads to poor dissolution & hence variation in bioavailability. The purpose of present investigation was to formulate and evaluate controlled release floating capsules of ciprofloxacin with improved solubility & dissolution rate. In present study granules using various carriers like mannitol & lactose indifferent ratios were prepared by wet granulation method using polymer such as ethyl cellulose & HPMC. The prepared granules were evaluated to preformulation studies such as angle of repose (18.41-24.22), bulk density, tapped density, compressibility index (11.31-12.75) & hausner's ratio. All the parameters shows that the granules having good flow properties. These granules had converted into the capsule forms. Then the formulated capsules were taken to the evaluation studies such as weight variation, release study, buoyancy & floating duration (more than 6 hrs.). We can conclude that all the parameters were within the acceptable limits.

Keywords:- *Controlled release, floating, capsules, Ciprofloxacin, buoyancy*

1. Introduction

Oral ingestion is the most convenient & commonly employed route of drug delivery due to its ease of administration, high patient compliance, cost effectiveness, least sterility constraints & flexibility in the design of dosage form. It was used to enhance the solubility of poorly soluble drugs [1,2]. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as generic development. The poor solubility & low dissolution rate of poorly water soluble drugs in the aqueous gastrointestinal fluids often cause insufficient bioavailability. Especially for class II (low solubility & high permeability) substances according to the BCS, the bioavailability may be enhanced by increasing the solubility & dissolution rate of the drug in the gastrointestinal fluids. As for BCS class II drugs rate limiting step is drug release from the dosage form & solubility in the gastric fluids & not the absorption, so increasing the solubility in turn increases the bioavailability for BCS class II drugs[3,4]. Adrug with poor bioavailability is the one with

- Slow dissolution rate & poor bioavailability in biologicalfluids.
- Poor permeation through biomembrane with inadequatepartition coefficient.
- Poor stability of dissolved drug at physiological pH.
- Extensive presystemic metabolism.

Few literature were comes up with improved solubility of some poorly water soluble drugs[5,6]

1. Enhancement of dissolution profile of meloxicam using solid dispersion with various polymers. Solid dispersion was prepared by melting & solvent evaporation method. Dissolution studies were performed for plain meloxicam, SD's & tablet formulations. Infrared spectroscopy & differential scanning calorimetry were performed toidentify the physicochemical interaction between drug & carriers.
2. Solid dispersion of furosemide in SSG was prepared in ratios of 1:1 & 1(furosemide): 2 (SSG) by kneading method. Dissolution studies indicated that the solid dispersion formulated in 1:2 ratios showed a 5.40-folds increase in dissolution & also exhibited superior dissolution characteristics to commercial furosemide tablets.

2. Materials & methods

Ciprofloxacin was obtained as a gift sample from Cipla Pvt. Ltd. (Goa, India). Mannitol, Lactose, Dichloromethane, Hydrochloric acid, Cetyl alcohol, Ethyl cellulose, HPMC, Sodium Bicarbonate, starch & Talc were procured from Pallav Chemicals, Mumbai. All materials used were of analyticalgrade.

2.1 Preparation of granules

Ciprofloxacin, Ethyl cellulose, HPMC, Cetyl alcohol & sodium bicarbonate were weighed by electronic balance & mixed well in mortar. Required amount of starch was taken in a beaker. Small amount of water was taken in it & stirred well until thick paste was formed without limps. Excess water was boiled in a separate beaker for 15 minutes & then add to the paste while stirring to form a mucilage. The mucilage was slowly added to the powder mix to form a damp mass that breaks with a snap when pressed between thumb & index finger. The damp mass was passed through the sieve & the granules were collected on dry tray. The granules were dried in hot air overate 60 °C for 2 hrs. Then the dried granules were passed through sieve. The granules were filledin empty gelatin capsules shell by hand filling capsules machine. The compositions of different ratios of floating capsules with different carriers are given in following tables [7,8,9],

2.2 Evaluation of granules flow characteristics[10,11,12]

Bulk density

A known quantity of granules were poured into the measuring cylinder carefully level the granules without compacting, if necessary & read the unsettled apparent volume (V), to the nearest graduated unit. Calculate the bulk density, in gm per ml, by the formula m/v.

Tapped density

A known quantity of granules were taken in a measuring cylinder & tapped on mechanical tapping apparatus for 5minutes. The initial 7 final volumes were noted.

Tapped density =volume of granules/final volume after tappig

Angle of Repose

The frictional forces in a loose powder or granules can be measured by angle of repose. This is maximum angle possible between the surface of pile of powder or granules & the horizontal plane. The value of angle of repose are calculatedby using the following formula,

$$\theta = \tan - 1(h/r)$$

h = Height of heap

r = Radius of the heap

Compressibility index & hausner's ratio[13,14]

The compressibility index closely related hausner's ratio has become the simple, fast & popular method of predicting granules flowcharacteristics. The compressibility index & hausner's ratio were determined both the bulk density & tapped density of granules.

Hausner's ratio = TD/BD

Composition of ciprofloxocin capsules

Table no. 1: Composition of ciprofloxacin floating capsules

Ingredients	F1	F2	F3	F4	F5	F6
Ciprofloxacin(mg)	100	100	100	100	100	100
Cetyl alcohol(mg)	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Ethyl cellulose(mg)	125	100	75	50	25	-
HPMC(mg)	-	25	50	75	100	125
Starch(mg)	15	15	15	15	15	15
Sodium bicarbonate(mg)	25	25	25	25	25	25
Talc(mg)	2.5	2.5	2.5	2.5	2.5	2.5

2.3 Evaluation of capsules Weight variation

Twenty capsules were randomly selected & individually weighed. The average weight of capsules were calculated & compared with individual weight.

2.4 Determination of In-Vitro dissolution study

Dissolution study was carried out in USP- II type dissolution apparatus (paddle type). Dissolution study was performed at 50 rpm in 900 ml 0.1 N HCL 5ml of sample was withdrawn at predetermined intervals & the volume of dissolution medium was maintained by adding same volume of dissolution medium. Absorbance of these solutions was measured using UV visible spectrophotometer.

2.5 Floating capacity

Floating characteristics of the prepared formulations were determined by using USP- II paddle type apparatus at a paddle speed of 50 rpm in 900 ml of a 0.1 N HCL solution (pH= 1.2) at 37 ± 0.5°C for 12 hrs. The time between introduction of capsule & its buoyancy on the simulated gastric fluid (floating time) & the time during which the dosage form remains buoyant (floating duration) were measured.

3.Results & discussion

Ciprofloxacin was estimated by UV spectrophotometer method by measuring the absorbance at 277 nm. The method was validated for linearity, accuracy, precision & interference. The method obeyed Beers law in the concentration range of 1-5 µg/ml (R^2=0.997)

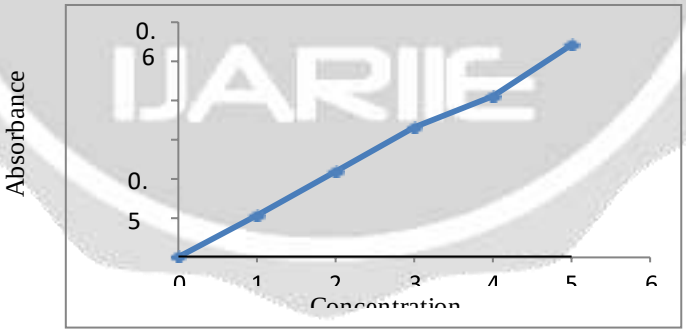

Figure no. 1: Calibration curve of ciprofloxacin in 0.1 N HCL

3.1 Preliminary solubility study

Table no. 2: Preliminary solubility studies of drug

S.NO	Drug: carrier	Solubility (µg/ml)
1	Pure drug	4.7
2	Ciprofloxacin + Mannitol	9.57
3	Ciprofloxacin + Mannitol	11.41
4	Ciprofloxacin + Mannitol	14.53
5	Ciprofloxacin + Lactose	20.51
6	Ciprofloxacin + Lactose	27.23
7	Ciprofloxacin + Lactose	31.89

In case of drug initially preliminary solubility analysis were carried out to select the appropriate water soluble carriers for the preparation of granules in which pure drug solubility found to be 4.7 mcg/ml. From this Mannitol and Lactose in the ratio of 1:1, 1:2, 1:4 was selected for the preparation of the granules. Complete composition of six formulations showed. The preliminary solubility study of ciprofloxacin was carried out for pure form as well as for drug: carrier mixture forms as shown in table no. 2. The solubility of pure ciprofloxacin was found to be 4.7 mg/ml. The preliminary solubility for drug: mannitol ratios 1:1, 1:2, 1:4 was observed 9.57 mg/ml, 11.41 mg/ml and 14.53 mg/ml respectively. On another hand, drug: lactose ratios 1:1, 1:2, 1:4 respectively showed 20.51 mg/ml, 27.23 mg/ml, 31.89 mg/ml preliminary solubility. The drug: lactose ratio 1:4 showed higher solubility as compared to drug: mannitol ratio 1:4

3.2 Evaluation of Solid dispersion granules

Micromeritic & morphological study of granules

In the present investigation, ciprofloxacin controlled release floating capsules were prepared by using polymers such as ethyl cellulose (EC) & HPMC. A total number of 6 formulations were prepared by wet granulation method. Angle of repose for F1-F6 is between 18.41° to 24.22°, bulk density is in between 0.442-0.450, compressibility index is in between 11.235-12.751 & Hausner's ratio is in between 1.126-1.146 are within the acceptable limits (table no:3). The above values are of precompression parameters show the prepared granules having good flow property. From the preformulation studies for drug excipients compatibility, it was observed that no physical incompatibility existed between the drug & excipients. The weight variation was within ±5 %, it waswithin the acceptable limit.

Table no. 3: Evaluation of Ciprofloxacin Granules (Ratio = 1:4)

Formulation	Angle of repose	Bulk density	Tapped density	Compressibility index(%)	Hausner's ratio
F1	18.41	0.392	0.442	11.312	1.127
F2	23.19	0.395	0.445	11.235	1.126
F3	17.35	0.390	0.447	12.751	1.146
F4	20.22	0.393	0.444	11.486	1.129
F5	22.30	0.395	0.449	11.026	1.136
F6	24.22	0.395	0.450	11.555	1.130

Table no 4: Evaluation of Ciprofloxacin Capsules Ratio (1:4)

s.no	Buoyancy lagtime (Sec)	Floating duration (hrs)
F1	27	>6
F2	48	>6
F3	51	>6
F4	36	>6
F5	45	>6
F6	58	>6

The floating duration was greater than 6 hrs in F1-F6 (Table no. 8). The formulation F6 showed higher buoyancy lag time as well as floating duration than others as showed in table no. 8.

3.3 In Vitro dissolution study of formulated capsules

In-vitro drug release showed (Figure no. 2) that the variation of release pattern of different batches (F1-F6) of the ciprofloxacin in 6 hrs study period. In-Vitro dissolution study was carried out for ciprofloxacin solid dispersion controlled release floating capsules. The % drug release has showed in table no. 5. The F6 showed 53.86 % drug release at 360 minutes, which is higher than % drug release of others. Formulation F6 showed higher solubility profile.

Table no. 5: In Vitro dissolution study of ciprofloxacin capsules (Ratio = 1:4)

Time (Min)	F1	F2	F3	F4	F5	F6
60	21.01	22.86	24.56	27.86	29.32	31.58
120	22.56	24.86	28.96	30.45	32.56	36.34
180	24.81	27.61	31.56	35.68	37.96	43.08
240	26.56	29.76	35.07	39.05	42.63	46.89
300	28.82	31.45	36.89	41.56	46.03	49.89
360	29.98	34.89	39.91	45.63	49.05	53.86

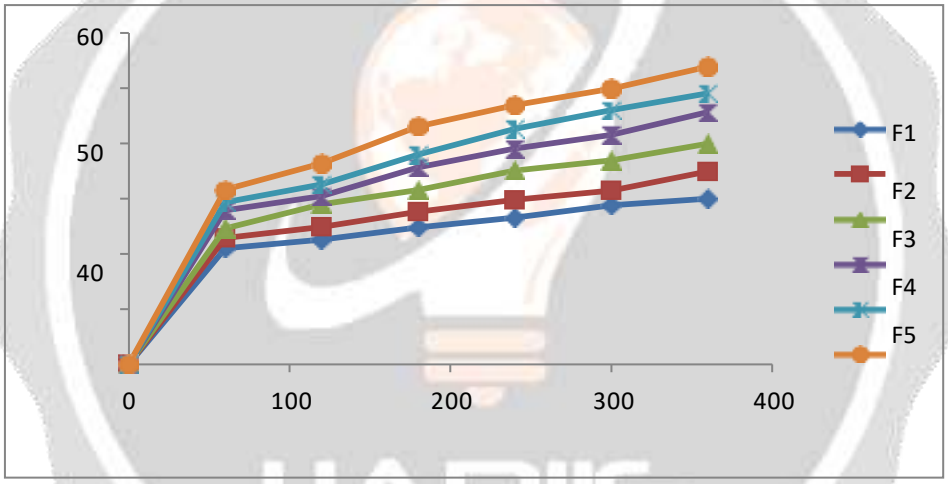

Figure no. 2: In Vitro dissolution study of formulated capsules

4. Conclusion

Granules prepared by wet granulation method using polymer such as ethyl cellulose & HPMC. It was effective in improving drug dissolution. These capsules were analyzed for solubility & in vitro dissolution profile. Dissolution of drug increase with an increase in carrier content. Granules prepared with lactose had shown enhanced solubility with improved dissolution rate. Controlled release floating capsules of ciprofloxacin & different carriers can enhance the gastric residence time as well as bioavailability & better patient compliance can be achieved.

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