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OPTIMIZATION OF CONTROLLED RELEASE GASTRORETENTIVE BUOYANT TABLET WITH XANTHAN GUM AND POLYOX WSR 1105

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The aim of present work was to prepare gastroretentive floating tablets containing Ofloxacin (OFX), an anti-bacterial agent. Floating tablets were prepared by direct compression using Sodium carbonate and citric acid as gas forming agents. Various grades of hydroxypropyl methyl cellulose (HPMC) were employed as swellable polymer. Xanthan gum and Polyox WSR 1105 were used as gelling agents for controlled release in combination with HPMC. The prepared blends were evaluated for precompression characteristics including angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio to assess flowability and compressibility. The tablets were evaluated for hardness, friability, swelling index, *in vitro* buoyancy and *in vitro* drug release. Results show that tablet blends were having good flow characteristics and compressibility. Percent swelling was ranging from 92.1 to 108.4, indicating excellent swelling property. The floating lag time of prepared tablets was found to be satisfactory in a range from 20 sec to 3 min 20 sec, while floating duration of all prepared batches was more than 24 hr. Formulations showed polymer concentration dependent drug release retardation over a period of 12 hrs.

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1. Introduction

The design of oral controlled drug delivery system should be primarily aimed at achieving more predictable and increased bioavailability of drugs. A major constraint in oral controlled release drug delivery is that not all drug candidates are absorbed uniformly throughout the gastro intestinal tract. Some drugs are absorbed in a particular absorption window. After crossing absorption window, the released drug gets wasted with negligible or no absorption. Thus the time available for drug absorption drastically decreases. Also most of the drugs are sparingly soluble or insoluble in gastric fluids. In such drugs, dissolution and bioavailability are directly dependent on time available for solubilization and thus gastric retention time. Thus bioavailability of such drugs can be increased by prolonging the gastric retention time.[1]

Gastro-retentive drug delivery system increases the gastric residence time of drug providing a better opportunity for increased solubilization and bioavailability. Also it can help in controlling the drug release rate by using various swellable polymer systems. Various approaches of gastro-retention are available viz. bioadhesive dosage forms, floating drug delivery by density based approach or effervescent system etc. Several reports are available stating the success of gastro-retentive drug delivery systems.[2, 3]

Ofloxacin is a synthetic broad-spectrum antimicrobial agent for oral administration and it is mostly used for local treatment for GI infection. It has short half life of 4-6 hr. Ofloxacin is

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reported to be absorbed from the acidic pH in the proximal part of the gastrointestinal tract and shows decreased absorption from the alkaline medium in the intestinal region. Thus increasing the gastric retention time of Ofloxacin can be helpful in increasing its bioavailability.[4]

The present work describes formulation of gastro-retentive drug delivery system for Ofloxacin by floating approach and evaluation for various pharmaceutical properties.

2. Materials and methods

2.1 Materials

Ofloxacin complying with USP monograph supplied by Zhejiang Apeloa Kangyu Pharmaceutical Co. Ltd was used in the study. HPMC (Methocel K4M, K15M, and K100M grades) suitable for use in the present study was supplied by Colorcon. Xanthan Gum (Ziboxan PM200) used was purchased from Deosen Biochemical Ltd Polyethylene oxide (Polyox WSR 1105) was obtained from Dow Chemicals ltd. All other excipients used were of pharmaceutical grade.

2.2 Preparation of ofloxcin floating tablets

The formulations containing HPMC along with Xanthan gum and Polyox WSR 1105 were prepared by direct compression method. Ofloxacin along with all the excipients except sodium bicarbonate, citric acid anhydrous and magnesium stearate were first sifted through sieve no. 30 and mixed well. Sodium bicarbonate and citric acid were sifted separately through sieve no. 60. Magnesium stearate was sifted through sieve no. 40. The drug blend was mixed with sodium bicarbonate and citric acid and then subsequently mixed with magnesium stearate. The blend was directly compressed into capsule shaped tablets on Erweka single station tablet press.[5]

Optimization of Gas Forming Agent:

Different formulation trials (Table 1) were taken using HPMC K100M (hydrophilic polymer) and Xanthan gum (gelling agent) for optimization of amount of sodium bicarbonate and citric acid. The tablets were made by using direct compression process. Compression was carried on Erweka single station tablet press using caplet shaped punches.

Optimization of polymer combination:

Various polymer combinations were prepared for optimizing the composition of the formulation. Three grades of HPMC were used in combination with Xanthan gum (SX1-SX9) and Polyox WSR 1105(SP1-SP12). The prepared trial batches are presented in Table 2 and 3.

Table 1: Optimization of Gas forming agent

Ingredients	**Composition in mg/tab**		
	SS1	**SS2**	**SS3**
Ofloxacin	400	400	400
HPMC K100 M	200	200	200
Xanthan Gum	40	40	40
Sodium bicarbonate	40	56	72
Citric acid	28	40	52
Lactose monohydrate	36	48	20
Magnesium stearate	16	16	16
Total	800	800	800

Table 2: Formulations with combination of HPMC and Xanthan gum

Ingredients	Composition in mg/tab								
	SX1	**SX2**	**SX3**	**SX4**	**SX5**	**SX6**	**SX7**	**SX8**	**SX9**
Ofloxacin	400	400	400	400	400	400	400	400	400
HPMC K100 M	200	160	120	-	-	-	-	-	-
HPMC K15 M	-	-	-	200	160	120	-	-	-
HPMC K4 M	-	-	-	-	-	-	200	160	120
Xanthan Gum	40	40	40	40	40	40	40	40	40
Sodium bicarbonate	72	72	72	72	72	72	72	72	72
Citric acid	52	52	52	52	52	52	52	52	52
Lactose monohydrate	20	60	100	20	60	100	20	60	100
Magnesium stearate	16	16	16	16	16	16	16	16	16
Total	800	800	800	800	800	800	800	800	800

Table 3: Formulations with combination of HPMC and Polyox WSR 1105

Ingredients	Composition in mg/tab											
	SP1	**SP2**	**SP3**	**SP4**	**SP5**	**SP6**	**SP7**	**SP8**	**SP9**	**SP10**	**SP11**	**SP12**
Ofloxacin	400	400	400	400	400	400	400	400	400	400	400	400
HPMC K100 M	200	160	120	80	-	-	-	-	-	-	-	-
HPMC K15 M	-	-	-	-	200	160	120	80	-	-	-	-
HPMC K4 M	-	-	-	-	-	-	-	-	200	160	120	80
Polyox WSR 1105	40	40	40	40	40	40	40	40	40	40	40	40
Sodium bicarbonate	72	72	72	72	72	72	72	72	72	72	72	72
Citric acid	52	52	52	52	52	52	52	52	52	52	52	52
Lactose monohydrate	20	60	100	140	20	60	100	140	20	60	100	140
Mg stearate	16	16	16	16	16	16	16	16	16	16	16	16
Total	800	800	800	800	800	800	800	800	800	800	800	800

2. 3. Evaluation of ofloxcin floating tablets:

Precompression Study:

The blends prepared using various compositions were characterized for the precompression characteristics for evaluation of flow properties and compressibility. The parameters include angle of repose, bulk and tapped densities, Carr's index, Hausner's ratio.[6]

Tablet Evaluation:

Prepared floating tablets were evaluated for various official and special evaluation parameters viz. appearance, hardness and friability. Hardness of the tablets was tested using Monsanto hardness tester for each trial and expressed in kg/cm^2. Friability of the tablets of each batch was determined by using Veego friabilator operated for 100 revolutions at the speed of 25 rpm. The tablets were then dusted and reweighed for the calculation of friability.[6]

***In -Vitro* Buoyancy Study:**

In vitro buoyancy is characterized by floating lag time and total floating duration.[7] The study was carried out using USP dissolution apparatus Type II using 900 ml of 0.1N HCl. at 50 rpm maintained at 37±0.5°C. The time required for tablet to rise to the surface of the dissolution medium was recorded as floating lag time and the duration of the time the tablet constantly floated on the dissolution medium were noted for each formulation trial.

Swelling Study:[8]

The swelling of the polymers can be measured by their ability to absorb water and swell enormously. The water uptake study of the tablets was performed using USP dissolution apparatus Type II in 900 ml of 0.1N HCl. at 50 rpm maintained at 37±0.5°C. The tablets were weighed and placed in the medium under rotation and withdrawn after selected time interval, excess water was removed by blotting. Tablets were weighed at each interval. The swelling index was given by following formula-

$$\%\ Swelling = \frac{Weight\ of\ swollen\ tablet\ -\ Initial\ weight\ of\ tablet}{Initial\ weight\ of\ tablet} \times 100$$

***In vitro* Dissolution Study:**

In vitro release study of Ofloxacin tablets was performed in USP dissolution apparatus Type II. The dissolution was carried out using 900 ml of 0.1N HCl maintained at 37 ± 0.5°C as dissolution medium constantly agitated at 50 rpm. 2 ml of aliquot was withdrawn at predetermined time intervals maintaining the sink condition. The samples were analyzed by UV-spectrophotometry (Jasco V-630, Japan) at 294 nm after suitable dilutions.[4]

3. Results and discussion

Optimization of Gas Forming Agent:

It was found that as the concentration of effervescent mixture increased from 5-7%, the floating lag time decreased and floating duration increased. Thereafter there was no change in floating duration. Therefore the 9% of sodium bicarbonate and 6.5% citric acid were chosen so as to get the possible shortest lag time and floating duration of up to 24 hours.

Precompression Study:

Table 4 describes the precompression characteristics of the prepared blends. The results show that angle of repose of all batches range from 27.34 to 31.47 indicating good flowability. It can be seen from Hausner's ratio and Carr's index that the formulation blends possess good compressibility and flow rates.

Table 4: Precompression characteristics of blend

Batch	Precompression characteristics				
	Angle of repose	**Bulk density g/ml**	**Tapped density g/ml**	**Carr's index**	**Hausner's Ratio**
SX1	31.47	0.480	0.623	23.03	1.299
SX2	30.62	0.484	0.628	22.86	1.296
SX3	28.82	0.491	0.635	22.59	1.292
SX4	29.98	0.496	0.643	22.81	1.296
SX5	29.50	0.483	0.627	22.97	1.298
SX6	28.39	0.485	0.639	24.07	1.317
SX7	29.27	0.491	0.623	21.21	1.269
SX8	28.82	0.486	0.625	22.17	1.285
SX9	27.96	0.491	0.630	22.00	1.282
SP1	30.62	0.498	0.623	20.11	1.252
SP2	30.22	0.502	0.631	20.48	1.258
SP3	28.39	0.496	0.638	22.22	1.286
SP4	27.96	0.488	0.616	20.70	1.261
SP5	31.21	0.480	0.601	20.15	1.252
SP6	30.46	0.489	0.633	22.70	1.294
SP7	28.82	0.478	0.611	21.79	1.279
SP8	27.37	0.484	0.623	22.43	1.289
SP9	29.05	0.492	0.631	22.04	1.283
SP10	30.62	0.488	0.630	22.46	1.290
SP11	28.82	0.493	0.619	20.31	1.255
SP12	27.34	0.483	0.631	23.55	1.308
FO1	29.50	0.494	0.630	21.54	1.275
FO2	28.82	0.492	0.633	22.24	1.286
FO3	27.75	0.489	0.622	21.33	1.271
FO4	29.05	0.479	0.613	21.83	1.279
FO5	28.82	0.482	0.630	23.50	1.307
FO6	28.17	0.486	0.623	21.98	1.282
FO7	27.96	0.481	0.616	21.92	1.281
FO8	29.27	0.484	0.619	21.70	1.277
FO9	29.05	0.491	0.638	22.98	1.298

Tablet Evaluation:

As shown in Table 5, Hardness of all the batches ranges from 5 to 7 which suggesting good tablet integrity. The friability of the formulations was found to be within the range o 0.08 to 0.37%, thus complying with the pharmacopoeial limits.

In -Vitro Buoyancy study

In vitro buoyancy is the most important evaluation parameter, as it specifies the main objective. It can be observed (Table 5) that the Floating lag time of the prepared tablets ranged from 20 sec to 3 min 20 sec. Thus it shows efficient buoyancy. The tablets were floating for the period of more than 24 hr ensuring retention of the drug delivery system till complete drug release will be achieved.

Swelling Study

Swelling is an important property required for sustaining the drug diffusion from the polymer matrix. As depicted in table 5, percentage swelling of the prepared tablets was ranging from 92.1 to 108.4, which indicate excellent swelling characteristics. This can be attributed to cellulosic matrix containing swellable polymer *viz*. HPMC of various grades.

Table 5: Tablet Properties

Batch	Tablet evaluation				
	Hardness (kg/cm^2)	**Friability**	**% Swelling**	**Floating lag Time (sec)**	**Floating duration hr**
SS1	-	-	-	40	3
SS2	-	-	-	22	24
SS3	-	-	-	65	24
SX1	6	0.25	108.4	90	24
SX2	6	0.25	105.7	58	24
SX3	7	0.24	102.3	190	24
SX4	5	0.29	100.1	115	24
SX5	7	0.36	99.8	200	24
SX6	7	0.19	101.7	57	24
SX7	6	0.27	97.8	165	24
SX8	7	0.33	98.1	75	24
SX9	6	0.23	97.4	120	24
SP1	7	0.13	103.3	42	24
SP2	7	0.15	104.9	39	24
SP3	5	0.08	106.3	27	24
SP4	7	0.11	102.9	32	24
SP5	6	0.11	100.1	35	24
SP6	7	0.14	99.8	29	24
SP7	6	0.09	101.7	22	24
SP8	6	0.13	96.5	26	24
SP9	5	0.13	97.8	38	24
SP10	5	0.11	95.7	32	24
SP11	4	0.17	93.5	26	24
SP12	5	0.18	92.6	26	24
FO1	7	0.26	92.1	21	24
FO2	7	0.33	93.0	45	24
FO3	6	0.33	92.8	51	24
FO4	6	0.21	93.5	36	24
FO5	7	0.36	93.7	20	24
FO6	7	0.22	92.9	20	24
FO7	5	0.37	95.1	24	24
FO8	6	0.25	93.9	48	24
FO9	5	0.23	94.2	30	24

***In vitro* Dissolution study**

The dissolution profiles of the prepared batches are shown in Fig 1 and 2. It can be observed that the drug release from the tablet is dependent on the nature as well as the concentration of polymer used in the formulation. The drug release was also found to be dependent on the gelling agent used. It can be seen from the release profiles that the drug release at 24 hr in case of xanthan gum formulations were in the range of 54.88- 81.41%. While the cumulative dissolution of drug from the tablets with Polyox were observed to be from 67.71 to 96.61%. Release of Ofloxacin was more retarded in all cases with HPMC K100M than HPMC K15M and HPMC K4M.The prolongation in drug release time can be attributed to the increasing viscosity of the polymer HPMC and swelling capacity. The increase in swelling causes increase in path length of diffusion which leads to decrease in release. As a result of increasing concentration of HPMC in the formulation, retardation in drug release was observed which can be attributed to concentration dependent viscosity changes in the swollen matrix. Thus the floating tablets of Ofloxacin using

gelling agents like Polyox and xanthan gum in combination with various grades of cellulosic polymer like HPMC were found to be effective to sustain the drug release up to 1 day.

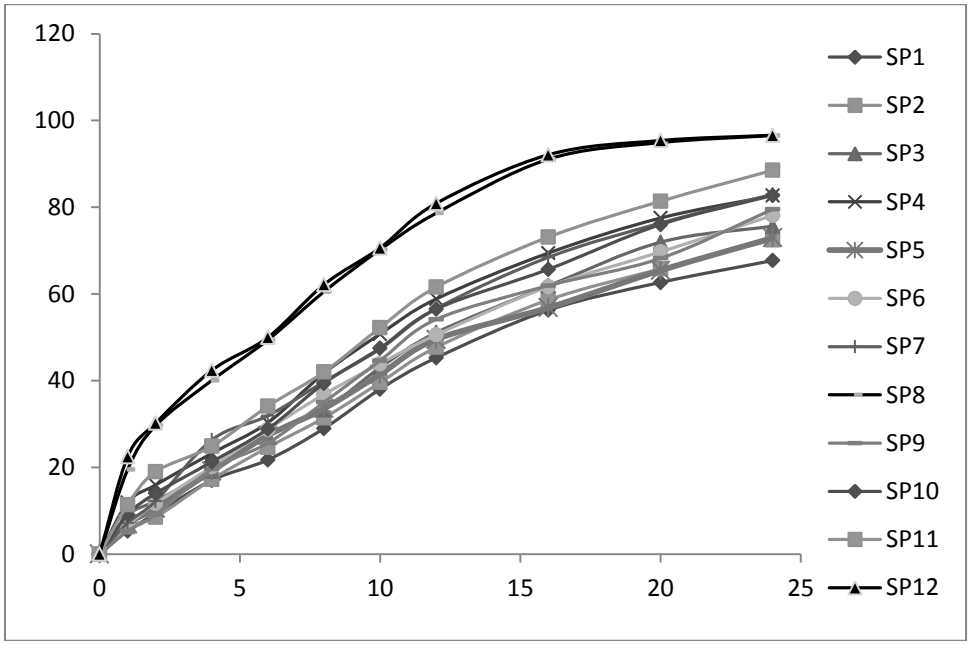

Fig 1: Dissolution profiles of batches with Polyox

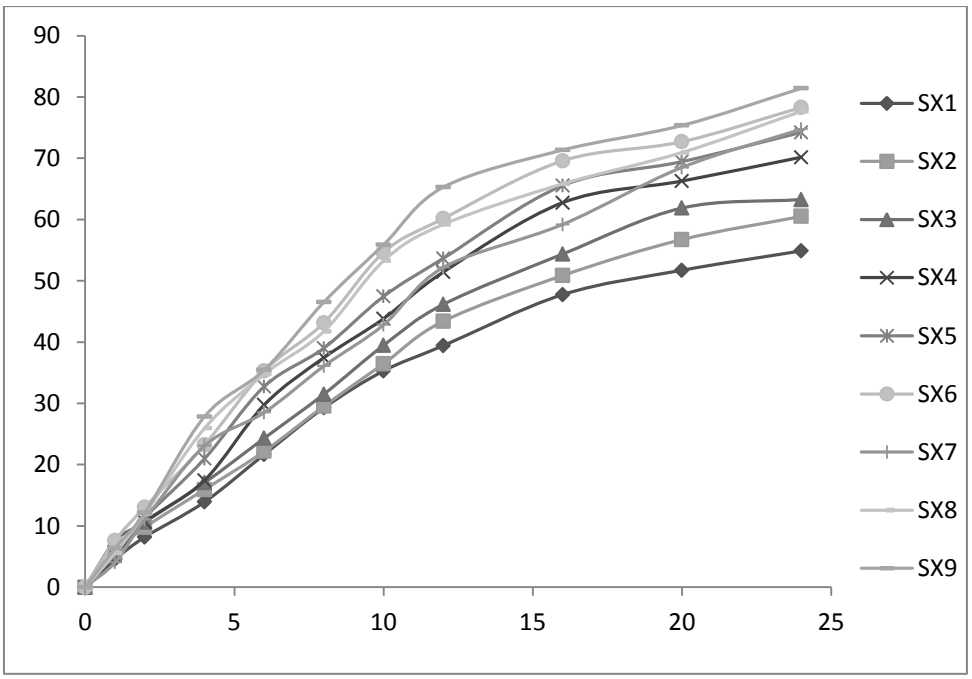

Fig 2: Dissolution profiles of batches with xanthan gum

4. Conclusion

In the current study, floating tablets of Ofloxacin were formulated with HPMC of various grades using Xanthan gum and Polyox as swelling agent. Both gelling agents were found to be efficient to cause swelling of the dosage form. Tablets were effectively buoyant along with the ability to retard the drug release. The technique can be industrially viable and useful in the effective antibacterial therapy with Ofloxacin.

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