Omdurman Journal of Pharmaceutical Sciences

https://journal.oiu.edu.sd/index.php/ojps

Formulation and Optimization of Ciprofloxacin Hydrochloride 500mg Floating Tablets

Sara Anas S.K[1*], Abd ElKarim M.A.K.[1], Eltayeb Suliman E.[1], Salah Mohamed Elhasan[2]

[1] Omdurman Islamic University, faculty of Pharmacy, Department of Pharmaceutics

[2]National Board of Medicines and Poisons

[*] Corresponding author *drsaraanassk@gmail.com*

DOI 10.52981/ojps.v2i2.2169 ISSN: 1858-506X

Abstract

Floating tablets of ciprofloxacin Hydrochloride was formulated as controlled gas powder system (CGPS) firstly by dry method which is found to by not suitable for bad micrometric properties of the powder bed, so these properties were improved by wet massing off powder using isopropanole as granulating liquid. The floating lag time (FLT) and total floating time (TFT) and release rate were optimized by different trials namely using the binder poly vinyl pyrelidone (PVP) in solution form, increasing the hydrophobic lubricant used, substitution of viscolyzing agent by other polymers, and then increasing its percentage and finally increasing percentage of viscolyzing components, PVP, sodium bicarbonate and the total tablet weight. The formula of the last step was of the best properties.

Keywords: Floating, viscolyzing agent, Buoyancy, Hydrophobic.

1. Introduction:

1.1. Floating drug delivery systems

Gastroretentive dosage forms are able to remain in the gastric region for several hours and hence significantly prolonging the gastric residence time of drugs and so improve bioavailability, reduce drug waste, and improve solubility of drugs that are less soluble in a high pH environment, it is also suitable for local drug delivery to the stomach and proximal small intestines [1]. Numerous strategies have been used to increase the residence time of the dosage forms in the stomach including mucoadhive systems, high density systems, swelling systems and floating systems [2]. The floating drug delivery systems (FDDS) are designed in such a manner that they floated to prolong gastric residence time, resulting in longer total transit time within the gastrointestinal tract environment with maximum absorptive capacity and consequently greater bioavailability[3]. Several formulation parameters can affect the gastric residence time including ; size of floating dosage forms [4] the units of multi particulate systems are distributed freely throughout the gastro intestinal tract so their transport is affected to a lesser extent by the transit time of food compared with single unit formulation. The size and shape of dosage units also affect the gastric emptying. Garg and Sharma [5] reported that tetrahedron and ring shaped devices have a better gastric residence time as compared with other shapes, dosage forms having a diameter of more than 7.5 mm show a best gastric residence time. The density of dosage units also affects the gastric emptying rate, buoyant dosage forms having a density of less than that of the gastric fluids floats away from the pyloric sphincter and hence it is retained in the stomach for a prolonged period [3], [6].

Type of Floating Drug Delivery Systems (FDDS):

FDDS are classified into non effervescent, gas generating (effervescent) and controlled gas powdered (non-effervescent) systems. Gas generating (Effervescent) systems utilizes matrices prepared with swellable polymers, polysaccharides and effervescent components. Upon arrival in the stomach, this system releases carbon dioxide and causing the formulation to float in the stomach [7]. Controlled gas powdered system (CGPS) provides a combination of spatial and temporal control of drug delivery to a patient for effective therapeutic results, the pharmaceutical composition comprises an active ingredient , a gas generating component, a swelling agent, a viscolyzing agent, and optionally a gelling polymer [8].

1.1.2. Manufacturing of FDDS:

FDDS can be prepared by conventional methods of preparing the tablets which include the dry

methods [8] and wet massing [9]. They are formulated mainly from an active substance, a swelling agent, a strong gelling agent, a weak gelling agent, optionally a diluents, anti static agents, a binder, a gas generating agent, binder alcohol (ethyl alcohol or isopropyl alcohol) or an alcohol and water mixture to provide granules [9].

1.1.3. Some factors affecting the formulation of FDDS:

1.1.3.1. Viscosity: The drug release rate is dependent on the viscosity and concentration of the polymer used in formulation, so formulation of floating tablet using high concentration of viscolyzing agent and/or polymers of high viscosities have slowest release rates compared to those formulated using low concentrations of viscolyzing agent and/or polymers of low viscosities [10].

1.1.3.2. Tablet Hardness: Buoyancy of tablets is governed by both the swelling, hydration, of the hydrocolloid particles on the tablet surface when it contacts with the gastric fluid which results in an increase in bulk volume, and presence of internal voids in the dry center of the tablet, porosity) [10], [11].

1.1.3.3. The ratio of drug to binder: The ratio of drug to binder such as PVP can affect the in vitro drug release, in such a way that increasing the amount of PVP result in significant acceleration of drug release profile, and decreasing drug: PVP ratio from 1:2 to 1:4 increases the drug release by 1.6 folds, this might be better explained in terms of the enhanced drug solubility caused by PVP [11].

1.1.3.4. Presence of Hydrophobic Agent: The presence of hydrophobic agent such as magnesium stearate in the formula could significantly improve the floating capacity of FDDS [12]

1.1.4. Characterization of FDDS:

FDDS as a pharmaceutical dosage forms are tested for their quality. They must meet the pharmacopoeial standards of the Content uniformity, Hardness and Friability tests [13]. The test for floating time is usually performed, the test is done to measure both the time taken by the dosage form to float (floating lag time FLT), and the time for which the dosage form floats (total floating time TFT) [14]. Dissolution and release rate is an important test done using dissolution apparatus for at least 6 hours [15]. Specific gravity (density) of the floating system can be determined by the displacement method using benzene as a displacing medium [16], [17].

This study aims to formulate and evaluate Ciprofloxacin Hydrochloride floating tablets as controlled gas powder system (CGPS), and to optimize the formulation to improve the floating properties (FLT and TFT), and percentage of drug released per time by deferent methods.

2. Materials and methods

2.1.Materials

Ciprofloxacin HCl.H_2O was purchased from (HIRAN ORGOCHEM, LTD India,). Sodium alginate and Iso propanole were from (SURECHEM PRODUCTS LTD). Xanthan gum and Poly Vinyl Pyrrolidone were from (ALPHA CHEMIKA). Sodium bicarbonate was from (CENTRAL DRUG HOUSE (P) LTD). Magnesium stearate and Talc Powder were from (TECHNO PHARMCHEM). Hydrochloric Acid and Benzene were from (ROMIL LTDSOURCE CONVENT DRIVE WATERBEACH CAMBRIDGE)

2.2. Methods:

2.2.1. Formulation of Controlled Gas Powered System (CGPS):

2.2.1.1. Selection of suitable method for preparation of CGPS

Ciprofloxacin 500 mg tablets was formulated as controlled gas powered system (CGPS) using formula given in table below [8], the stated amounts of powder ingredients were mixed using high shear mixer for 5 minutes. About 20 gm were lubricated with 50% of magnesium stearate (0.41 gm) and mixed thoroughly for 5 minutes using mortar and pestle, then slugged using 20 mm die, another 20 gm were wet massed using 10ml iso propanole and screened through 850 mic mesh, the resultant granules were allowed to dry, equal weight was wet massed using 10 ml of distilled water and screened through the same mesh, the resultant granules were also allowed to dry.

ingredie	**Ciprofloxa HCl.H_2O**	**Sodiun algina**	**Xanth gum**	**Sodium bicarbon**	**PVP**	**Magnesi stearate**	**Talc**
Weight	69.9%	0.3%	1.03%	1.03%	12.15%	2.25%	0.68%

2.2.1.1.1. Characterization of powders:

The flowability and compressibility characteristics of the powder mixtures were tested by weighing 20 gm of the mixture and measuring its bulk volume using 100 ml measuring cylinder, and the corresponding density was calculated as bulk density, and after tapping for 5miniuets the tapped volume was measured and the corresponding density was calculated as tapped density, then Hausnar ratio and compressibility percentage were calculated using equations (1) and (2) respectively [18].

$$\text{Husnar ratio} = \frac{\text{True density}}{\text{Bulk density}} \quad \ldots\ldots\ldots (1)$$

$$\text{Compressibility\%} = \frac{\text{True density} - \text{Bulk density}) * 100\%}{\text{True density}} \quad \ldots\ldots\ldots (2)$$

2.2.1.2. Formulation of (CGPS) by wet massing using iso propanole:

A batch of 100 tablets was prepared by wet massing using iso propanole as follows; the required quantities of components were weighed and mixed using high shear mixer for 5 minutes. Iso propanole was added gradually during mixing for 10 minutes to get a damp mass, screened by the wet granulator and the resultant granules were allowed to dry at room temperature [19]. The size of resultant granules was adjusted to 500 μ mish, lubricated using talc and magnesium stearate and mixed thoroughly by tumbling in a large container for 5 minutes. The lubricated mixture was compressed by the single punch machine using die 13 mm after adjusting machine to give weight of 802 mg and hardness approximately 4kp.

2.2.1.2.1. Quality control tests of (CGPS) tablets

a. Physical tests

Weight variation, hardness and friability tests were carried out on the formulated tablets as described in USP [20].

b. Buoyancy test

This test was designed to calculate floating lag time (FLT) which is the time required for the tablet to float in dissolution medium, and total floating time (TFT) which is the total time during the tablet stay floated, using 0.1N HCl in USPII dissolution tester rotated at 50 rpm [16].

c. Tablet density

Tablet density was tested by displacement method in benzene [16] as described below: 50 ml of benzene was placed in a measuring cylindar, 1 tablet was weighed and placed in

benzene the rise in volume withdrawn by 2 ml pipette and used as tablet volume to calculate the density by equation (3).

$$Tablet\ Density = \frac{Weight\ of\ tablet}{Volume\ of\ tablet} \quad \ldots\ldots (3)$$

d. In vitro drug release

To measure the release rate of the drug from the dosage form, USPII apparatus was used to calculate the percentage concentration released hourly for 3 tablets using 900 ml of 0.1N HCl as dissolution medium, mounted at 50 rpm and maintained at body temperature; hourly 10 ml of the dissolution medium was taken for each tablet and replaced with fresh medium [21], and 5ml of the sample were diluted with 0.1N HCl to100ml, and analyzed with UV-VIS spectrophotometer at wave length 277 nm [22]. Cumulative percentage of drug release was calculated and the mean of the 3 tablets was used in data analysis. The dissolution study was continued for 6 hours [23]. Single point calibration method was used to estimate the rate of release of drug from the dosage form. A standard solution was prepared by dissolving 582.2 mg of ciprofloxacin HCl.H_2O powder in 900 ml of 0.1N HCl, 5 ml of the solution were diluted to 100 ml using 0.1N HCl and analyzed as above; its reading was used as a standard. Three readings were taken for each sample and their mean was used to calculate the percentage release using single point calibration method according to equations (4), (5) and (6).

$$\frac{concentration\ of\ sample}{concentration\ of\ standard} = \frac{absorbacnce\ of\ sample}{absorbance\ of\ standard} \quad \ldots\ldots\ldots\ldots\ldots\ldots (4)$$

$$\text{Amount dissolved} = \frac{absorbacnce\ of\ sample}{absorbance\ of\ standard} * \frac{concentration\ of\ standerd}{900\ ml} \quad \ldots\ldots\ldots (5)$$

$$\text{Amount dissolved \%} = \frac{amount\ dissolved}{500\ mg}\ 100\% \quad \ldots\ldots (6)$$

2.2.2. Optimization of (CGPS) formulation

a. Optimization by wet massing using binder solution

Another method of wet massing was tried, instead of using PVP as dry powder it was dissolved in iso propanole to make a binder solution. Two batches were prepared; the first was prepared by dissolving the whole amount of PVP , used in formula, in iso propanole to form granulating liquid (F 2), and the other was formed by dissolving (50%) of PVP in isopro panol and the rest amount was used as dry powder blend (F3). And thence the formulated tablets were evaluated.

b. Optimization by increasing the percentage of Magnesium Stearate and reducing Sodium Bicarbonate

For further increase of the TFT lubricant "magnesium stearate" which is hydrophobic material was increased to be used in its upper limit (5%) of the total tablet weight, and sodium bicarbonate was reduced to be 8.9% using 100% and 50% PVP binder solutions (F4, F5).

c. Optimization by substituting the viscolyzing agent

i. Viscosity measurement for different viscolyzing agents

Firstly 1 % (w/v) aqueous solutions or dispersions were prepared of xanthan, guar gum, tragacanth and acacia, and the viscosity of each one was measured using rotational viscometer. Different concentrations of mixtures of guar: acacia (1:9-9:1) respectively were prepared, 1% (w/v) aqueous solution was prepared for each one, and the mixtures viscosities were measured by the same viscometer.

ii. Formulation of optimized formula by substituting viscolyzing agent

In order to improve the release rate and TFT, xanthan was substituted with guar gum, and mixtures of guar: acacia in concentrations of 8:2 and 9:1. Twelve batches were formulated, four batches of each (guar gum (F6,F7, F8,F9), and mixtures of guar: acacia 8:2 (F10,F11,F12,F13) and 9:1(F14,F15, F16, F17)). In the first 100% of PVP used in the formula was dissolved in iso propanole and magnesium stearate represented 2.26% of tablet weight, in the second 50% of PVP used in the formula was dissolved in iso propanole and 50% of it was used as dry powder and magnesium stearate represent 2.26% of tablet weight i.e. substitution of xanthan, in the third 100% of PVP used in the formula was dissolved in iso propanole and magnesium stearate represent 5% of tablet weight and in the fourth 50% of PVP used in the formula was dissolved in iso propanole and 50% was used as dry powder and magnesium stearate represent 5% of tablet weight.

iii. Optimization of the formula by increasing the percentage of viscolyzing agent:

In order to increase the total floating time, the formula was changed by increasing the mixture of viscolyzing agents (xanthan as viscolyzing or strong gelling agent, and sodium alginate as film forming polymer or weak gelling agent) to be 5% of the total weight of the tablet, the ratio between them is 3:1 respectively and reducing both of PVP and sodium bicarbonate to 9.86% of the total weight of the tablet (802.2 mg). A

batch of the new formula (F18) was prepared by dry mixing of the drug with sodium alginate, xanthan gum and sodium bicarbonate, and dissolving the entire amount of PVP in iso propanole and the produced tablets were tested for their quality.

iv. Optimization of the formula by increasing percentage of viscolyzing components, PVP, sodium bicarbonate and the total tablet weight:

For furthermore improvement of tablet two batches were formulated by increasing the percentage of the viscolyzing components, PVP and sodium bicarbonate in ratio (1:1) to be 15% of the total of the tablet which is also increased to be 850 mg (F19) and 950 mg (F20), while the percentages of magnesium stearate and talc were maintained approximately constant.

3. Results:

3.1. Results of powder characterization:

Powder/granules	Powder mixture	Lubricated mixture	Iso propanole granules	Water granules
Hausnar ratio	1.63	1.59	1.11	1.12
Compressibility%	38.78%	1.59	10.51%	11.14%

3.2. Results of quality control tests of tablets:

3.2.1. Results of physical, density and buoyancy tests of formulae F1 –F5:

Test	F1	F2	F3	F4	F5
Weight variation test **Deviation%**	1.65	2.04	1.99	2.163	1.744

Hardness test(kp)	4.64	7.75	7.74	5.35	5.01
Friability test (Loss %)	0.73	0.68	0.85	0.33	0.68
Tablet density test (mg /ml)	0.918	0.915	0.997	0.921	0.917
FLT(sec)	21	27	23	24	22
TFT(min)	27	32	30	75	73

3.2.2. Results of dissolution and release test of F1 –F5:

Time hours	**Release %**				
	F1	**F2**	**F3**	**F4**	**F5**
1	82.22	77.59	81.54	60.78	72.29
2	84.05	81.93	85.43	75.85	75.69
3	84.86	81.99	85.69	80.74	79.07
4	87.14	83.25	86.27	81.45	86.11
6	89.81	85.12	87.27	84.88	91.22

3.2.3. Results of viscosity test of different viscolyzing agents:

3.2.3.1. Results of viscosity test of individual polymers:

Viscolysing agent	**Gum Guar**	**Xanthan**	**Tragacanth**	**Acacia**
Spindle	L3	L3	L1	L1
RPM	20	60	200	200
Viscosity	1412	140	7	6

3.2.3.2. Results of viscosity test of mixtures of (guar : acacia):

G:A	1:9	2:8	3:7	4:6	5:5	6:4	7:3	8:2	9:1
Spindle	L1	L1	L1	L1	L1	L1	L2	L2	L3
RPM	200	200	200	100	100	60	100	60	60
viscosity	8	10	20	30	39	42	140	380	890

3.2.4. Results of quality control tests of tablets Formulated by substituted viscolyzing agent:

3.2.4.1. Results of physical, density and buoyancy tests of formulae F6 –F18:

Formula No	Wight variation (D%)	Hardness (kp)	Friability (Loss%)	Tablet density (mg/ml)	FLT (sec)	TFT (min)
F6	2.23%	6.24	0.29%	0.993	20	88
F7	3.74%	5.31	0.18%	0.986	21	84
F8	2.22%	4.193	0.006%	0.991	24	90
F9	1.84 %	4.33	0.86%	0.985	23	86
F10	1.66%	6.96	0.91%	0.988	26	65
F11	1.42%	5.96	0.35%	0.984	24	68
F12	3.46%	4.09	0.69	0.982	22	61
F13	1.61%	4.21	0.44%	0.991	23	63
F14	2.54 %	5.90	0.19%	0.987	23	70
F15	1.29 %	5.72	0.19%	0.992	25	73
F16	1.234%	4.002	0.95%	0.989	24	72
F17	1.183%	4.23	0.76%	0.985	22	75
F18	0.71%	5.36	0.08%	0.989	23	2:14

F19	1.47%	5.86	0.26%	0.989	15	2:57
F20	1.982%	5.98	0.174%	0.989	10	>6:00

3.2.4.2. Results of dissolution test of F6 –F20:

Time hours	**Release %**						
	F6	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
1	70.65	76.12	69.81	66.57	64.89	64.19	50.36
2	71.61	77.72	71.84	75.95	70.80	66.15	64.45
3	74.02	80.84	72.81	78.36	73.85	67.11	68.56
4	81.3	81.77	76.43	79.49	78.18	70.39	70.91
6	83.57	85.21	79.14	81.22	85.66	71.23	72.67

Time hours	**Release %**							
	F13	**F14**	**F15**	**F16**	**F17**	**F18**	**F19**	**F20**
1	61.17	71.45	62.39	62.07	69.46	74.41	70.68	59.59
2	65.67	84.95	66.05	66.05	75.82	76.69	71.80	64.51
3	68.46	85.95	67.66	67.82	76.21	79.70	72.81	73.70
4	70.20	95.46	76.92	70.55	77.33	83.12	74.22	74.95
6	60.87	96.33	82.19	74.15	78.01	87.27	76.37	76.37

4. Discussion

In the present study the dry granulation by slugging was failed, so the granulation was shifted to wet massing. The granules prepared by wet massing using iso propanole as wetting agent were the best choice because they had the best flowbility and compressibility over the three powders (lubricated powder, water granules and iso propanole granules) referring to its Hausnar ratio and compressibility percentage

values(1.11and 10.51%) respectively which mean free flowbility and excellent compressibility [18].

The tablets of (F1) were completely destroyed in friability test and released ~ 82% of the drug in the first hour because the wetting agent “iso propanole” was used without binder and so it was of insufficient cohesiveness. This problem was solved in later batches by dissolving PVP in iso propanole to form binder solution (F2 and F3) with suitable cohesiveness, the amount of binder used ranged from 0 to 10% binder solution [9], the use of such a solution resulted in formulation of sufficiently strong tablets. Batches formulated by dissolving 50% of the used PVP in iso propanole were less strong than those formulated by dissolving the entire amount of PVP in iso propanole due to higher binding capacity of concentrated binder solution “100% of PVP used dissolved in iso propanole”, but the formulated systems were rabidly loosed their physical integrity, the total floating time “TFT” of the tablets were very short and the percentage drug released in the first hour was very high. (Li *et al* claimed that the presence of hydrophobic agent (e.g. magnesium stearate) could significantly improve the floating capacity of the delivery system[12], on this basis new batches were formulated by increasing the lubricant "Magnesium stearate" to be used in its upper limit used in tablet i.e. 5% of the total tablet weight, and reducing the gas generating component to maintain the total weight (F4 and F5), This resulted in an insignificant improvement of TFT (from 45 and 40 min to 50and 47 min) and the percentage drug release was relatively improved (from 72.65% and 76.72% to 60.78 and 72.29) respectively.

As the viscosity of the viscolyzing agent used in formulation of floating tablet is of great importance in the drug release rate [10], and the strong gelling agent or the viscolyzing agent is a compound presenting a viscosity of at least 600 centipoises when it is in the form of a 1% W/V aqueous solution at 25°C [9], the viscosities of 1% W/V aqueous solutions of different polymers that can be used as viscolyzing agent (xanthan gum, tragacanth gum, guar gum, and acacia) [8] were measured, tragacanth and acacia were excluded because they were of very low viscosities (6 and 7 Cp respectively) so they were not suitable to be used as viscolyzing agents, while gum guar, and xanthan were of high viscosities. Among this range of polymers the locally produced in Sudan are guar of the highest viscosity and acacia of the

lowest one, 9 mixtures of different concentrations of the two polymers (1:9 to 9:1 guar: acacia) were prepared and the viscosities of their 1% solutions were tested, solutions of 8:2 and 9:1 guar: acacia mixtures were of reasonable values. So guar and the two mixtures were used in the formulation as viscolyzing agents instead of xanthan gum.

To study the effect of the viscolyzing agents in the formula four batches of each polymer selected were prepared by substitution of xanthan in the formulae (F6-F17), these batches resulted in a slight improvement of both the release rate (between 61% and 71% of the dose released in the first hour) and the TFT (about 1.5 hour), but the tablets of the twelve batches were sank in the depth of the dissolution medium after few minutes of floating and this may be due to the relatively high densities of the tablets formulated using guar and the mixture of guar and acacia, or these tablets may have a negative resultant weight (the apparatus used in this test is not available)

All of the above formulated batches had fast release which is undesired in sustained release formulations and insufficient floating times as the flotation or retention time of gastro retentive formulations is related on the normal duration of emptying from the stomach in fed state (4 to 6 hours) following a meal [24]. These main two defects were found due to a very small percentage of viscolyzing components used in the formulae, they were used in 1.33% of the total weight of the formula, the actual total amount needed to be of both weak gelling agents and strong gelling agents ranges from 5 to 25% by weight of the total weight of the formulation, the ratio between them ranges from 1:3 to 1:5 [9]. In order to optimize the formula and improve TFT and release rate, a new formula was developed by increasing the viscolyzing components mixture (xanthan gum: sodium alginate 3:1) to be 5% of the total tablet weight and reducing both of PVP and sodium bicarbonate to be 9.86% (for each) of the total weight of the tablet (F18), this step resulted in a considerable increase in the TFT to be 2:14 hours , but it had little or no effect on the release rate (74.41% released in the first hour), this result may be due to the considerable reduction of PVP and sodium bicarbonate to percentage less than that stated in literature (sodium bicarbonate from about10% to about 30% by weight of the composition, and PVP from about10% to about 20% by weight of the composition) [8].

Further optimization of the formula was done by increasing both of the viscolyzing component mixture (xanthan gum: sodium alginate 3:1), PVP and sodium bicarbonate (1:1) to be 15% of the total weight of the tablet (F19 and F20) , in which viscolyzing mixture, PVP, and sodium bicarbonate were used within the preferred ranges stated in the literature [9] was the most appropriate one, it had TFT of more than 6 hours, and it released 58.50% of its dose in the first hour and 77.95% after 6 hours.

5. Conclusion:

It can be concluded that the starting formula was found containing very small amount of viscolyzing components, so it had very short TFT and fast release profile, and the formula that gave the best results is (F20). Substitution of xanthan with the guar and acacia resulted in tablets of relatively high densities sink in the dissolution media after their initial floating; this may be related to their resultant weight so their use as viscolyzing agents is not beneficial.

Acknowledgements:

With appreciations and sincere of thanks I acknowledge firstly ALLAH, then Dr. ElNazeer I. Hamed ElNiel to his encouragement and support, my great thanks are to Abu-Bakr M. Ahmed and Daowod Tag Eldeen for their grateful technical assistance and support where they did hardly during the practical work of this research.

REFRENCES

[1] Venkata Srikanth Meka, Senthil Rajan Dharmanlingam,Venkata Ramana Murthy Kolapalli: Formulation of gastroretentive floating drug delivery system using hydrophilic polymers and it's *in vitro* characterization, *Brazilian Journal of Pharmaceutical Sciences vol. 50,* 2014

[2] Nagi Reddy Dumpa, Suresh Bandari, Michael A. Repka: Novel gastroretintive floating pulsatile drug delivery system produced via hot melt extrusion and fused deposition modeling 3D printing, *Pharmacutics,* 2020.

[3] Shweta Arora, Javed Ali, Alka Ahuja, Roop K.Khar, and Sanjula Baboota: Floating Drug Delivery Systems: A Review, *AAPS PharmSciTech*, Article7, (2005)

[4] Timmermans J, Andre JM.: Factors controlling the buoyancy and gastric retention capabilities of floating matrix capsules: new data for reconsidering the controversy. *J Pharm Sci*, (1994).

[5] Garg S, Sharma S. Gastro retentive drug delivery systems. Business Briefing:

Pharmatech 2003 Web Site. 5th edition, (2005).

[6] Mirmeera Girish Niharika, Kannan Krishnamoorthy, Madhukar Akkala: Overview oo floating drug delivery system, *Int J App Pharm*, 2018.

[7] Mohamed HG Dehghan, Furquan N Khan: Gastro retentive Drug Delivery Systems: A Patent Perspective, *International Journal of Health Research*, (2009).

[8] Talwar, Naresh, Sen, Himadri, Staniforth, John N.: Orally administered controlled drug delivery system providing temporal and spatial control *U.S. Patent 6261601*, 2001.

[9] Mahendra Chaudhari, Omprakash D. Chandwani, Rajashree S.Yelegaonkar: Gastro retentive Formulations and Manufacturing Process Thereof, *Patent application number: 20080220060*, (2008).

[10] Abubakr O Nur, Jun S. Zhang: Captopril floating and/or bioadhesive tablets: Design and release kinetics, *drug development and idusterial pharmacy, volume 26*, issue 9, (2000).

[11] Suad.Y.Elkarib: Development, optimization and evaluation of Glabenclamide gastro retentive tablet formulation, *PhD thesis*, U of Khartoum, (2006).

[12] Li S, Lin S, Daggy BP, Mirchandani HL, Chien TW. : Effect of formulation variables on the floating properties of gastric floating drug delivery system. *Drug Dev Ind Pharm.* (2002).

[13] Agnihotri S.A., Jawalkar S.S. and Aminabhavi T.M., Controlled release of cephalexin through gellan gum beads: Effect of formulation parameters on entrapment efficiency, size, and drug release, *Eur. J.Pharm. Biopharm.*, (2006).

[14] Garima Chawla, Piyush Gupta, Vishal Koradia, and Arvind K. Bansal, Gastro retention, A Means to Address Regional Variability in Intestinal Drug Absorption: *Pharmaceutical Technology,* (2003).

[15]Mukesh C. Gohel, Pavak R.Mehta, Rikita K. Dave and Nehal H. Bariya: A More Relevant Dissolution Method for Evaluation of Floating Drug Delivery System, *Dissolution Technologies*, (2004).

[16] Rosa M, Zia H, Rhodes T. Dosing and Testing In-Vitro of a bioadhesive and floating drug delivery system for oral application. Int.J.Pharm 1994; 105: 65-70. 45. Sangekar S., Evaluation of effect of food and specific gravity of the tablets on gastric retention time, *Int.J.Pharm*, (1987).

[17] Sangekar S., Evaluation of effect of food and specific gravity of the tablets on gastric retention time, Int.J.Pharm, 35(3), 34-53,

(1987). 46. Sarojini S., Arivazagan D., Manavalan R., Jayanthi V.: Buoyant sustained release tablets based on Polyethylene oxide. *International Journal of Pharmacy and Pharmaceutical Sciences,* Vol 2, Suppl 1, (2010).

[18] Aulton M.E.: Pharmaceutics, *the science of dosage form design*, second edition (2002).

[19] Dilip M. Parikh: *Handbook of Pharmaceutical Granulation Technology, Second Edition*, (2005).

[20] USP 32-NF 27, (2009).

[21] Kossmeyer R, Gurny R, Peppas N. Mechanism of solute release from porous hydrophilic polymers. *Int.J.Pharm*, (1983).

[22] Isabel Pascual-Reguera, Gertrudis Perez Parras and Antonio Molina Diaz: Solid-phase UV spectro photometric method for determination of ciprofloxacin, *Int.J.Pharm*, (2004).

[23] Mofizur Rahman Md., Sumon Roy, Sreedam Chandra Das, Mithilesh Kumar Jha, Md. Qamrul Ahsan, Md. Shahparan, Md. Selim Reza: formulation and evaluation of hydroxy propyl methyl cellulose based matrix systems as oral sustained release drug delivary systems for ciprofloxacin hydrochloride, *International Journal of Pharmaceutical Sciences Review and Research*, Volume 6, Issue 2, (2011).

[24] Baumgartner, S., Tivadar, A., Vrecer, V., and Kristl, J.: Development of floating tablets as a new approach to the treatment of Helicobacter pylori infections. *Acta Pharm*., (2001).