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RESEARCH

COMPARATIVE STUDY OF VARIOUS GASTRORETENTIVE APPROACHES

Mansi Gulati*, Anupama Diwan, Supriya Mor

Deparment of Pharmaceutics, Hindu College of Pharmacy, Sonepat, Haryana

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Corresponding Author:
Mansi Gulati,
Deparment of Pharmaceutics, Hindu College of Pharmacy, Sonepat, Haryana
gulati.mansi05@gmail.com

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ABSTRACT

Present study is aimed to evaluate the influence of polymer content and polymer type on the release profile of drug. In this invention, gastroretentive controlled release platform was developed based on three approaches that is raft, matrix based on KollidonSR and Xanthum gum and Bigranular approach.. All these approaches used sodium bicarbonate as the gas generating medium for creating the buoyancy that led to gastric retention. Ciprofloxacin Hydrochloride has been selected as model drug. It is highly water soluble drug with an absorption window at upper jejunum with dose of 598.47 mg. Out of the three approaches tried, even with low compression forces tablets of astonishing hardness has been obtained with Kollidon SR and Xanthum gum matrix based approach. Even results of biphasic gastro retentive delivery was also satisfactory, but, raft approach was not proved its stance to the extent of matrix based approach. The time of flotation was 620 min. and the drug release was sustained for 18 hrs and hence the optimized systemic control of 24 hrs with matrix based GR approach. Drug loading was achieved to be more than 60%. Polymer to drug ratio was achieved with lowest possible content of 16-17%. The Kollidon SR and Xanthum gum matrix based approach could prove to be the best among the three approaches tried.

INTRODUCTION

This study generally relates to novel pharmaceutical compositions for oral administration, in particular to gastro– retentive controlled released system for delivery of **Ciprofloxacin hydrochloride** that exhibit a "small absorption window" in gastrointestinal tract. That is, they are more effectively absorbed only from stomach, duodenum and initial portion of small intestine. Hence, it is mandatory to retain the drug in stomach for extended period of time. Therefore gastro-retentive controlled release approach is most appropriate for such type of drug candidate. The efficiency and patient compliance of these API's and similar candidates can be improved by retaining them in stomach for longer time and hence, can acquire uniform continuous release of the same in a controlled manner. It is also desirable to avoid the initial lag time in the release of antibiotic from controlled release composition hence the pharmaceutical compositions of the present inventions designed to have an initial loading dose as an immediate release form.

The matrix system is commonly used for manufacturing sustained release dosage forms because it makes manufacturing easy. Wide arrays of polymers viz hydrophilic, hydrophobic and plastic matrix system have been widely used. Plastic matrix system, due to their chemical inertness and drug imbedding ability have been widely used for sustaining the release of drug . Liquid penetration into the matrix is the rate limiting step in such system unless channeling agents are used. The hydrophobic and waxy materials, on the other hand, are potentially erodable and control the release of the drug through pore diffusion and erosion disintegrate, but immediately after hydration develops a highly viscous gelatinous surface barrier which controlled the drug release from and liquid penetration into the center of the matrix system.

The objective of this work is to evaluate the influence of polymer content and polymer type on the release profile of drug as well as to establish a relationship between drug retaining efficiency of the polymer and physiochemical properties of the drug. Kollidon SR (polyvinyl acetate and polyvinyl pyrrolidone based matrix forming agents), Xanthum gum and hydroxy propyl methyl cellulose (HPMC-K100M) have been selected as the representatives of plastic hydrophobic and hydrophilic matrix system respectively.

Gastro retentive controlled release platform was developed based on:-

a) Raft approach
b) Matrix based controlled release approach
c) Biphasic gestro retentive approach

All these approaches used sodium bicarbonate as gas generating component. **Ciprofloxacin Hydrochloride** has been selected as model drug. It is highly water soluble

drug with an absorption window at upper jejunum with dose of 598.47 mg.

EXPERIMENTAL

Preliminary trial experiments were performed for the selection of variety of excipients chosen for the formulation development strategy alone or in combinaton with drug of designed period of floating time and drug release characteristics. In order to achieve this goal, exicipients with promising floatable and release retardants properties were selected. A number of derivative of cellulose polymeric substances as release retardants excipients with floatation capabilities were tested namely Sodium carboxymethyl cellulose and ethylcellulose. Different grades of synthetic polymeric compounds like Hydroxy propyl methyl cellulose , ethyl cellulose, xanthum gum were also identified for their delayed release and development of floatable dosage forms. Ciprofloxacin hydrochloride, a highly soluble fluroquinoline antibiotic alone did not show any floating tendencies and therefore was required in the formulation which could control its drug release and floatation capabilities.

Improvement of the properties of granules in terms of strength, solubility and compression was done by employing following means :-

a) Addition of binder 4 – 5% w/w PVPk 30 to the granulation solvent of IR granules and incorporation of HPMCk100M (15 – 18% w/w) to the granulation solvent of GR granules.
b) The other rate controlling polymer ethyl cellulose was added extra granular to the dried GR granules.
c) The granulation solvent is isopropyl alcohol.
d) Kollidon SR based formulations have been directly compressed, as it is a good directly compressible vehicle. The granules were compressed on a 16 station rotor press.
e) The tablets are tested for dissolution in 0.1 N Hcl using USP apparatus I at 100 rpm.

I) Raft approach

A novel delivery base was designed and developed to explore the possibility to achieve sustained delivery through floatable tablet. Besides swellable polymer, sodium alginate was incorporated in the formulation design as it exhibits excellent swelling and hydration capability in the formulation which allow the acidic solvent front to penetrate the matrix due to rapid hydration of tablet and generate CO_2 gas inside the polymeric core. Different formulations were prepared to contain both sodium alginate and sodium bicarbonate, other ingredients added were microcrystalline cellulose as diluent of direct compressible nature, magnesium stearate as lubricant and aerosil as disintegrant. The polymeric network in tablet was formed of sodium alginate crosslinked with carbonate and xanthan gum. The average weight of tablet made was in range of 910-930mg. These granules were also evaluated for the determinaton of micromeritic and derived properties. Some of them were bulk density, tapped density, Hausuer ratio and Compressibility index.

II) Development of Kollidon SR matrix based gastroretentive approach

A new base of floatable tablet was explored and innovation was in its design formulated with advanced exicipients, Kollidon SR, an exicipient for drug delivery matrices consisting of polyvinyl acetate (8 parts w/w) and polyvinyl pyyrrolidone (2 parts w/w) possesses good controlled release properties. It has good flow properties and dry binding activity which provide easy handling and effective development and production of sustained release tablets by direct compression method. Weighed quantity of Kollidon SR, was mixed with the formula specified amount of sodium bicarbonate, xantham gum and aerosil@ The formulations were designated as AD22 to AD25. Dry powder blend was filled in the die cavity of the 16-station tablet press and compressed to convex, 12 mm diameter tablet using oval shaped punches, with hardness of 10- 14 kg/cm^3. The tablets were physically evaluated to know its hardness, friability, disintegration and weight variation. Tablets were further characterized for floatability, and drug release determination.

III) Bi-phasic gastro retentive approach

This contains two different portions one which is immediate releasing part and another portion consist of a delayed release portion of dose. The immediate release fraction of the drug dosage was also prepared with desired characteristics. In this step an immediate release IR portion as ciprofloxacin granules was prepared which would be required for the later stage of experimentation for developing new formulations. For formulation of IR granules, the drug is granulated with IPA containing PVPk 30. The granules are oven dried and sieved from since no. 18 and bag mixed with lubricant. IR granules, wherever used, contain 30% the drug and 5% of PVP K 30 as binder. GR granules contains 10% of drug and 25% of polymer alone or in combination and 20% of gas generating component.

Matrix made of ethylcellulose shown to have enough mechanical strength which makes it impermeable to gas to be escaped from the granular matrix. As a result the gas would be remained inside the core of granule which causes the delivery device to float in the gastric secretion and showed gastro-retentive property. Ciprofloxacin Hcl as (active pharmaceutical ingredient) was admixed with aerosil 200, xantham gum and sodium bicarbonate and granulated with sufficient quantity of isopropyl alcohol to form wet mass which was passed through sieve no 12. Wetted granules were dried at 60^{o}C and further sized to sieve no 16. These granules along with Ciprofloxacin granules, microcrystallinecellulose (Avicel102), ethylcellulose and aerosil200 were blended. In bi-granular blend was further added povidone K-30 as dry binder. Final granular powder was filled in the die cavity of 16 -station tablet press and compressed to tablet using 12mm oval faced punches. The hardness of the tablet was kept in the range of 12 -14kg/cm2 and permissible average weight. Bigranular powder was evaluated to characterize for the determination of flow and other derived properties. Tablet was subjected to physical evaluation for hardness, friability, weight variation and disintegration test and for specific evaluation parameters to characterize floatability, buoyancy time determination and drug release profiles.

RESULTS AND DISCUSSIONS

I) Raft approach

Results from these experimentations showed granules were light, loosely packed, possessing higher intragranular volume and free flowing characteristic. In AD7, xanthan gum was incorporated in the formulation to enhance the floating behavior of tablets, which was around 3 hrs. Floatation time reached at maximum level to 4 hrs, on further addition of xantham gum as its amount reached to maximum of 50mg. Drug release was extended for the period of 8 hrs duration for AD6 & AD7 formulations.

II) Development of Kollidon SR matrix based gastroretentive approach

Tablets contained Kollidon SR compressed at higher forces showed floating tendency existed for more than 24 hours. It is due to the fact that matrix tablet made of Kollidon SR have low apparent density and of porous nature. Formulation of tablets was successfully prepared composed of increasing amount of Kollidon SR as AD22, AD23 and AD24 had 50, 100, and 150 mg of Kollidon SR respectively. The average weight of tablet was in the range of 700-800mg. The effect of Kollidon SR concentration in the formulation was also studied on release characteristics of tablet. A complete drug release lasted upto 3 hours in case of AD22, which was almost doubled in case of AD23 and took 8 hours as shown by AD24. Addition of other formulation factors namely gelling agent as xanthan gum and gas generating agent sodium bicarbonate in AD25 formulation (100mg) would enhanced the drug release and promoted the floating capability to 6hours. Drug release could be extended upto 10 hours when formulation incorporated doubled amount of xanthan gum alongwith crosscarmellose sodium as seen in AD26. It was attributed the effect of kollidonSR porous, capillar framework formation inside the tablet as result of compression force when granules was converted into tablet.

III) Bi-phasic gastro retentive approach

All formulation of this design strategy was successfully compressed into tablets to contain immediate releasing amount of apx. 200mg Ciprofloxacin hydrochloride which is equivalent to 33% of the drug contenet and maintaining dose of apx. 430mg (equivalent to 67% of the drug). The effect of ethylcellulose on tabletting, floatation and release characteristic of the tablet was taken into the design consideration and hence AD27 to AD30 combinations were fabricated. Tablets were rapidly disintegrated and large proportion of granules have been visually seen floatable and easily recognized as they colored the release medium pink. The result of this studies demonstrated that adopted formulation worked strategically and effectively. In vitro drug release experiment of AD27 showed that the release could be extended upto a period of 6 hours. Experimentation conducted to know their floating capability showed it could be floated for the period of 4 hours. The specific function of ethylcellulose to make an impermeable membrane around the granule, in order to retain the gas inside the core of granule. Their cumulative percentage drug release was found to be 94% in 10hrs, 100% in 24hrs and 93% in 24 hrs respectively. The buoyancy time observed in all formulation was found to be 10mins. Another formulation AD31 was formulated using 75mg of ethylcellulose and xanthan gum, which showed the complete drug release in 24 hours with 8 hours of floating time. The xantham gum not only contributes toward the floatability of the formulation but also it result in swelling of the sustained granules completely to release the drug from formulation.

Stability Studies:

After a thorough study of formulation factors in the preliminary work, four different prototype formulation compositions were able to produce matrix tablets within the target weight (i.e. , not to exceed 1.1g) having acceptable hardness values 10-16, excellent tablet-to-tablet reproducibility with respect to dissolution profiles and acceptable surface profile were selected as the benchmarks for furtyher development efforts. The two formulations AD19 and AD29 placed at accelerated stability conditions and evaluated. No significant change was found with respect to appearance, moisture, average drug content and dissolution.

SUMMARY &CONCLUSION

Various formulations based on three different approaches using three types of polymers viz, kollidon SR, Xanthum gum, HPMC k100M, alone or in combinations, have been prepared and evaluated for influence of the polymer content and polymer type on the release profile of drug and the drug retaining efficiency of the polymer was compared. Formulation based on HPMC/EC and Kollidon SR/Xanthum gum have shown comparative release profiles, however, the later formulation have floated in the system for long time. Thus compositions according to the present inventions donot only provide gastroretentive dosage forms which release active agents in a controlled manner through biphasic gastroretentive system but also provide initial instantaneous release of active agent avoiding delay in antimicrobial action.

The result generated in this study showed the profile and the kinetics of drug release was the function of polymer type, polymer level and physiochemical nature of the drug.

The invitro release was carried out in 0.1N Hcl and release was found to be sustained for 18 hrs and hence the optimized systemic control of 24 hrs. Time of floatation for5 HPMC based formulations have been optimized to be 480 min. and for Kollidon SR based formulation to be 640 min.the optimized formulation exhibited shelf life for 2 years. This is also concluded that raft approach is not a better approach to develop GR system of Ciprofloxacin Hydrochloride. For optimized matrix based and bigranular approach formulations the sodium bicarbonate has been forund most effective at concentration range of 25% (sodium bicarbonate to drug rratio) in achieving buoyancy for 6-10 hrs. This biphasic matrix system using Kollidon SR and Xanthum gum combination for gastroretentive approach appeared a better formulation strategy. Polymer to drug ratio was achieved with lowest possible content of 16-17% and drug loading was achieved to be more than 60%.

Table I Comparative cumulative drug release profile from different formulations made of swelling and effervescent tablet based on raft approach

Time (hrs)	Drug release in percentage Formulation Code				
	AD4	AD5	AD6	AD7	AD8
0 hr	0	0	0	0	0
1 hr	78	52	44	36	32
2 hr	100	75	54	49	44
4 hr		100	70	67	61
6 hr			90	86	80
8 hr			100	100	99

Figure1 Comparative drug release profile from tablets made by different formulations as shown in the table1

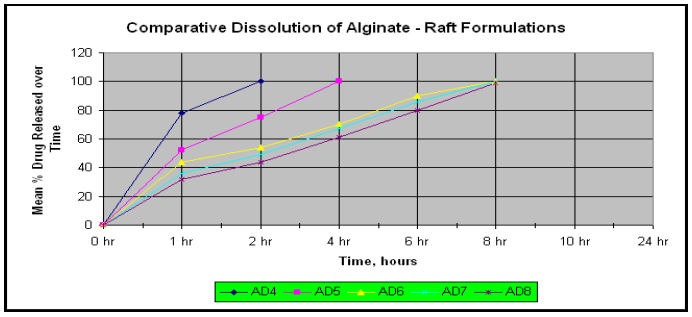

Table 2 Comparative cumulative drug release profile from different formulations made from the kollidon SR polymeric matrix

Time (hrs)	Drug release in percentage Formulation Code				
	AD22	AD23	AD24	AD25	AD26
0 hr	0.0	0.0	0.0	0.0	0.0
1 hr	55.0	42.0	34.0	32.0	29.0
2 hr	72.0	53.0	50.0	46.0	45.0
4 hr	100.0	76.0	72.0	66.0	63.0
3hr		97.0	86.0	78.0	72.0
8 hr		100.0	96.0	90.0	85.0
10 hr			100.0	100.0	100.0
24 hr					

Figure2 Comparative drug release profile from table 2

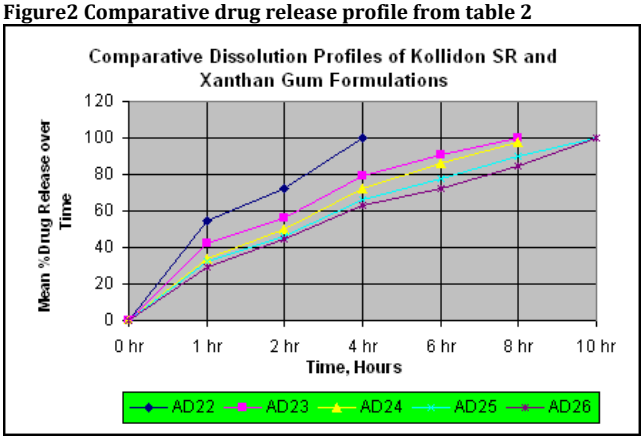

Table3: Comparative cumulative drug release profile from different formulations made from the biphasic polymeric matrix- a gastroretentive approach

Time (hrs)	Drug release in percentage Formulation Code				
	AD27	AD28	AD29	AD30	AD31
0 hr	0.0	0.0	0.0	0.0	0.0
1 hr	45.0	32.0	22.0	18.0	28.0
2 hr	60.0	46.0	34.0	26.0	44.0
4 hr	84.0	58.0	44.0	38.0	56.0
6 hr	100.0	70.0	58.0	52.0	72.0
8 hr		85.0	70.0	60.0	83.0
10 hr		94.0	82.0	71.0	96.0
24 hr		100.0	100.0	93.0	100.0

Figure3 Comparative drug release profile from tablets as shown in the table3

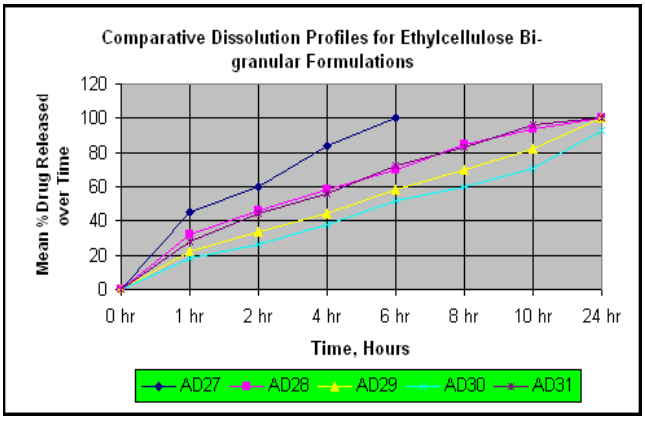

Table4:Comparative cumulative drug release profile obtained after stress testing from different selected formulations

Time (hrs)	Drug release in percentage Formulation Code				
	AD8	AD18	AD21	AD25	AD29
0 hr	0.0	0.0	0.0	0.0	0.0
1 hr	31.8	34.0	39.0	32.0	21.0
2 hr	42.9	50.0	48.0	45.0	33.0
4 hr	58.9	60.0	66.0	64.0	44.0
6 hr	77.8	72.0	74.0	80.0	55.0
8 hr	99.9	81.0	83.0	91.0	70.0
10 hr		97.0	96.0	99.9	79.0
24 hr		99.0	100.0		100.0

Figure4 Comparative drug release profile from tablets as shown in the table4

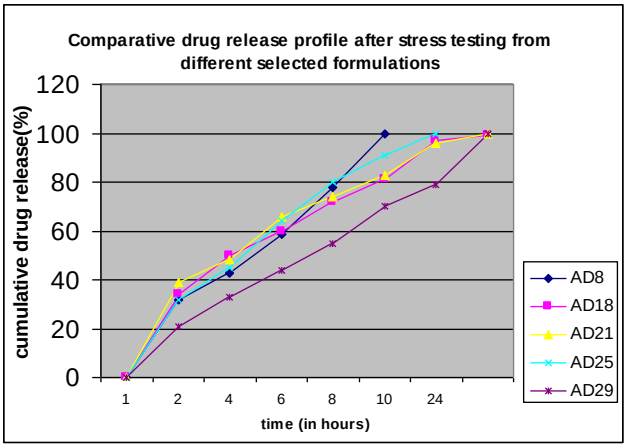

Table A Preparation of floatable tablets formulated with effervescent and swellable principles

Ingredient(mg)	Formulation code				
	AD4	AD5	AD6	AD7	AD8
Ciprofloxacin granules	630	630	630	630	630
Xanthan gum	-	-	-	25	50
Sodium alginate	50	75	100	100	125
Sodium bicarbonate	75	75	75	100	100
Calcium carbonate	25	25	25	25	25
Microcrystalline cellulose	100	100	100	100	100
Magnesium stearate	10	10	10	10	10
Aerosil	10	10	10	10	10
Total weight of Tablet	900	925	950	1000	1100

Table B Preparation of floatable tablets formulated using kollidon SR by direct compression method

Ingredient(mg)	Formulation code				
	AD22	AD23	AD24	AD25	AD26
Ciprofloxacin granules	630	630	630	630	630
Kollidon SR	50	100	150	100	100
Xanthan Gum	-	-	-	30	60
Sodium bicarbonate	-	-	-	100	80
Magnesium stearate	15	-	15	15	15
Aerosil	10	-	10	10	10
Total weight of Tablet	705	730	805	885	925

Table C Preparation of novel floatable tablets formulated using bi-granular Ciprofloxacin by direct compression method

Ingredient(mg)		Formulation code				
		AD27	AD28	AD29	AD30	AD31
Ciprofloxacin Hcl	Sustained releasing granules	540	540	540	540	540
Aerosil200		9	9	9	9	9
Xanthan Gum		-	-	-	-	30
Sodium bicarbonate		100	100	100	100	100
Coloring agent(pink)		1	1	1	1	1
Povidone-K30		5	5	5	5	5
Ethylcellulose		50	75	100	125	75
Isopropyl alcohol		q. s	q. s	q. s	q. s	q. s
Ciprofloxacin granules	Immediate releasing granules	63	63	63	63	63
Microcrystalline cellulose		100	100	100	100	100
Magnesium stearate		10	10	10	10	10
Aerosil200		10	10	10	10	10
Total weight of tablet		888	913	938	963	943

REFERENCES

1. Streubel , A. , Siepmann , J. , Bodmeier , R. , (2003) Floating matrix tablets and bead on low-density Foam powder: effects of formulation and processing parameters on drug release.*Eur. J. Pharm. Sci.* 18 , 37-45.
2. Dave, B.S. , Amin , A.F. , Patel , M.M. , (2004) Gastroretentive drug delivery system of ranitidine hydrochloride: formulation and *in vitro* evauluation. *AAPS Pharm. Sci. Tech*. 5,1-16.

3. Basak , S.C. , Nageswara Rao , K. , Manavalan , R. , Rama Rao ,P. , (2004) Development and *in-vitro* evaluation of an oral floating matrix tablet formulation of ciprofloxacin. *Ind. J.Pharm. Sci.* 66, 313-316.
4. Talukder , R. , Fassihi , R. , (2004) Gastroretentive drug delivery systems: hollow beads. *Drug. Dev. Ind. Pharm***.** 30 , 405-412.
5. Baumgartner , S. , Kristl , J. , Vrecer , F. , Vodpivec , P. , Zorko , B. , (2000) Optomisation floating matrix tablets and evaluation of their gastric residence time. *Int. J. Pharm***.** 195, 125-135.
6. Whitehead , L. , Collett , J.H. , Fell , J.T. , (2000) Amoxycillin release from a floating dosage form based on alginates. *Int. J. Pharm***.** 210 , 45-49.
7. Nur , A.O. , Zhang , J.S. , (2000) captoril floating and/ or bioadhesive tablets: design and release kinetics. *Drug. Dev. Ind. Pharm***.** 26 , 965-969.
8. Wei , Z. , Yu , Z. , Bi , D. , (2001) Design and evaulation of a two layer floating tablet for gastric retention using cisapride as a model drug. *Drug. Dev. Ind. Pharm***.** 27 , 469-474.
9. Sawicki , W. , (2002) Pharmacoknetics of verapamil and norverapamil from controlled release floating pellets in humans. *Eur. J. Pharm. Biopharm***.** 53, 29-35.
10. Li , S. , Lin , S. , Daggy , B.P. , Mirchandani , L. , Chien , Y.W. , (2003) Effect of HPMC and carbopol on the release and floating properties of gastric floating drug delivery system using factorial design. *Int. J. Pharm***.** 253 , 13-22.
11. Klausner , E.A. , Lavy , E. , Friedman , M. , Hoffman , A. , (2003) Expandable gastroretentive dosage forms. *J. Control. Release***.** 90, 143-162.