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Development and *In Vitro* Evaluation of Hydrodynamically Balanced System for Aceclofenac Delivery

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ABSTRACT

This work investigates the development and evaluation of hydrodynamically balanced systems (HBSs) of aceclofenac as single unit capsule. The various HBS capsules were formulated by physical blending of aceclofenac with carbopol 934, hydroxypropyl methyl cellulose, pectin in different ratios. These HBS capsules were evaluated for weight uniformity, drug content uniformity, *in vitro* floating behavior and drug release in simulated gastric fluids (pH 1.2). All these formulated HBS capsules containing aceclofenac were floated well over 5 hours with no floating lag time, and also showed sustained *in vitro* drug release in simulated gastric fluid over 5 hours. The aceclofenac release was found to be more sustaining with the addition of polymer i.e. carbopol 934 and hydroxyl propyl methyl cellulose. The drug release pattern of these aceclofenac HBS capsules (F-1, F-4, F-5 and F-8) were correlated well with first order model where F-6 to F-7 and F-2 toF-3 was correlated well with Higuchi model Korsmeyer-Peppas model with Fickian diffusion mechanism. All the experimental results showed that the aceclofenac HBS capsule successfully sustain the drug release along with improve the oral bioavailability of candidate drug.

Keywords: Hydrodynamically balanced system, gastroretention, aceclofenac, capsules.

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INTRODUCTION

Despite of several drawbacks, oral route is still considered as preferable route of drug administration and also extensively accepted as the first avenue investigated in the discovery and development of new drug entities and pharmaceutical formulations as because of patient acceptance, convenience, and cost effective manufacturing process [1].Over past few decades, various sustained or controlled drug delivery system have been developed to minimize demerits of oral drug delivery like variable gastric emptying and rapid gastrointestinal transit time which are further followed by incomplete drug release from the dosage form at absorption site in gastrointestinal tract lading to weaken efficacy of the administered dose [2].This has triggered to the development of gastroretentve drug delivery system that have been investigated and designed to confer prolong gastric residence time and optimal bioavailability of drug candidate [3].In gastroretentive drug delivery system, various approaches have been reported in literature for better improvement gastroretention in oral dosage form viz. floatation [4], mucoadhesion [5,6], sedimentation [7], unfoldable, expandable, or swellable systems [8], superporous hydrogel systems [9], magnetic systems [10], etc. Among them, Floating dosage forms are designed to be remained buoyant in stomach for several hours [11]. In gastroretentive floating system, hydrodynamically balanced systems (HBS_S) have received a great attention in order to provide better absorption of drugs having "narrow absorption window" [12]. These systems contain drug with gel forming hydrocolloids meant to remain buoyant for several hours in the stomach content. On contact with the gastric fluid, these systems form a water colloidal gel barrier around their surface and maintain a bulk density less than 1. They are mainly single-unit dosage forms, and usually composed of one or more gel-forming hydrophilic polymeric substances and an active pharmaceutical ingredient [13].

Aceclofenac which is a phenyl acetic acid derivative, 2-[(2, 6-Dichlorophenyl) amino] phenyl acetoxy acetic acid is used in the symptomatic treatment of pain and inflammation with a reduced side effect profile especially regarding gastrointestinal complications [14, 15].Aceclofenac enables to block prostaglandin E2 secretion at the site of inflammation by inhibiting IL-Beta and Tumour necrosis factor in the inflammatory cells. But, it has a short biological half life (about 4 hr) which makes it suitable candidate for the modified release dosage forms [16]. But, sustained delivery of aceclofenac may provide desirable serum concentrations for prolonged periods without frequent dosing, thereby providing patient compliance. In the present investigation, we have developed various HBS capsules of aceclofenac using HPMC K4M, carbopol 934 and

pectin for better delivery of aceclofenac by increasing the mean residence time in the GIT, which may provide maximum drug at the site of absorption to improve oral bioavailability

MATERIALS AND METHODS

Materials

Aceclofenac was a gift sample form Albert- David Pvt. Ltd., India. Carbopol 934 and pectin were obtained from B. S. Traders Pvt. Ltd., India. Hydroxypropyl methylcellulose (HPMC K4M) was purchased from Loba Chemie Pvt. Ltd., India. All other chemicals and reagents used were of analytical grade.

Preparation of aceclofenac HBS capsule

Aceclofenac HBS capsules were prepared by simple blending of 100 mg of aceclofenac and selected various polymers. Magnesium stearate (5 % w/w) as lubricating agent was added to the blend and mixed for additional 3 minutes. The final blend was filled into empty hard gelatin capsules (size 0) manually. Care was taken to fill the contents completely to maintain the uniformity of contents and weight. The composition of the HBS capsules is given in Table 1.

Table 1: Composition of various aceclofenac HBS capsule.

Formulation code	Drug (mg)	Carbopol (mg)	HPMC K4M (mg)	Pectin (mg)	Magnesium stearate (%)
F-1	100	100	100	0	5
F-2	100	100	50	50	5
F-3	100	100	25	75	5
F-4	100	100	0	100	5
F-5	100	50	50	100	5
F-6	100	25	75	100	5
F-7	100	75	100	25	5
F-8	100	0	100	100	5

Determination of weight uniformity

To determine capsule weight uniformity, 30 capsules were sampled and accurately weighed using an electronic analytical balence. The results were expressed as mean values of 30 determinations. The coefficient of variation was calculated using the formula:

Coefficient of variation (%) = Standard deviation / Mean × 100

Determination drug content

The aceclofenac HBS capsules of each formulation were dissolved in 0.1 N HCl with help of cosolvent. Samples were filtered using Whatmann® filter paper (No.40) and then, the drug content in the filtrate was determined spectrophotometrically of using a UV-visible spectrophotometer (Thermo Spectronic UV-1, USA) by measuring at $\lambda_{max,}$ 272 nm. Three replicate determinations were made for each formulation.

***In vitro* floating properties**

The capsules were immersed in 900 ml of in simulated gastric fluid, pH 1.2 in USP type II apparatus at 50 rpm maintained at 37 ± 0.5°C for 5 hours. The time for which the capsules constantly remain float on the surface of the medium (buoyant) was observed visually and was taken as the floating time.

***In vitro* drug release studies**

In vitro drug release studies were performed in USP type II apparatus (Campbell Electronics, India) at 50 rpm maintained at 37± 0.5°C. Various aceclofenac capsules were placed into the dissolution medium of 900 ml of simulated gastric fluid (pH 1.2). The 5ml of aliquots was withdrawn from the dissolution vessel at specific time intervals and replaced with equivalent volume of fresh medium. Collected dissolution samples were filtered using Whatmann® filter paper (No.40) and then, used for determination of released aceclofenac was determined spectrophotometrically of using a UV-visible spectrophotometer (Thermo Spectronic UV-1, USA) by measuring at $\lambda_{max,}$ 272 nm. Each *in vitro* release study was performed in triplicate.

Analysis of *in vitro* drug release kinetics and mechanism

To analyze the mechanism of drug release from these aceclofenac capsule matrices, the *in vitro* dissolution data were fitted to various mathematical models like zero order, first order, Higuchi, and Korsmeyer-Peppas models [17-20].

Zero-order Model: $F = K_0 t$, where F represents the fraction of drug released in time t, and K0 is the apparent release rate constant or zero-order release constant.

First-order Model: $\ln (1-F) = - K_{1st} t$, where F represents the fraction of drug released in time t, and K_1 is the first–order release constant.

Higuchi Model: $F = K_H t$, where F represents the fraction of drug released in time t, and K_H is the Higuchi dissolution constant.

Korsmeyer-Peppas Model: $F = K_P t^n$, where F represents the fraction of drug released in time t, K_P is the rate constant and n is the release exponent, this indicates the drug release mechanism.

Again, the Korsmeyer-Peppas model has been employed in the *in vitro* drug release behavior analysis of various pharmaceutical formulations to distinguish between various release mechanisms: Fickian release (diffusion-controlled release), non-Fickian release (anomalous transport), and case-II transport (relaxation- controlled release). When, $n \leq 0.5$, it is Fickian release. The n value between 0.5 and 1.0 is defined as non-Fickian release. When, $n \geq 1.0$, it is case-II transport and this involves polymer dissolution and polymeric chain enlargement or relaxation [20].

Mean dissolution time (MDT) is used to characterize the drug release rate from a dosage form and indicates the drug release-retarding efficiency of the polymer. In this study, MDT was calculated from dissolution data using the following formula [21]:

$$MDT = [n/n + 1] \times K_P^{(-1/n),}$$

Where n is the release exponent and K_P is the release rate constant.

RESULT AND DISCUSSION

The hard gelatin capsules filled with polymer and other excipients are generally used in oral drug delivery because of their ease of production facility, flexibility to obtain a desirable drug release profile, cost effective and broad regulatory acceptance [22-24].

Here, aceclofenac loaded HBS capsule were prepared along with various hydrocolloid polymers and evaluated for their in vitro performances.

The result of weight uniformity of these aceclofenac capsules is shown in Table 2. All these formulations met the USP specifications for weight uniformity. The mean weight of these formulated aceclofenac HBS capsules varied from 339.92 ± 7.05 to 342.82 ± 5.68 mg. The coefficient of variation of these capsules varied from 1.65 to 2.08 %. The values of coefficient of weight variations indicate that filling of capsules carried out properly. The drug content (%) within these aceclofenac capsules was determined and this was within the range between 97.82± 2.45 to 99.12± 3.15 % (Table 2).

Table 2: Weight uniformity and drug content (%) results of aceclofenac capsules.

Formulation code	Weight uniformity		Drug content (%)± S.D.*
	Mean weight ± S.D.* (mg)	Coefficient of variation (%) †	
F-1	341.92 ± 6.48	1.89	99.05± 3.05
F-2	341.05 ± 7.12	2.08	98.48± 2.83
F-3	339.92 ± 7.05	2.07	98.12± 3.12
F-4	342.82 ± 5.68	1.65	97.98± 2.12
F-5	340.55 ± 5.92	1.74	99.12± 3.15
F-6	342.08 ± 6.89	2.01	98.82± 2.54
F-7	341.44 ± 7.05	2.06	97.82± 2.44
F-8	340.45 ± 6.28	1.84	98.68± 2.68

*S.D. = Standard deviation,

†Coefficient of variation (%) = Standard deviation / Mean × 100

This result confirms that the uniform mixing of aceclofenac with other ingredients. All these HBS capsules containing aceclofenac were evaluated for *in* vitro floating behavior in 900 ml of in simulated gastric fluid, pH 1.2 in USP type II apparatus at 50 rpm maintained at 37 ± 0.5°C for 5 hours. They were floated well with no floating lag time. The floating time of these aceclofenac HBS capsules were more than 5 hours. This may be accounted to increased gel

strength of the polymeric combination matrices with drug in the form of HBS capsules. The mechanism involved in buoyancy of these HBS capsules, could be rapid hydration and swelling of the polymeric matrices producing a floating mass in the gastric pH (1.2). The swelling of the polymeric chains could be increased with an increase of polymer viscosity, but the highly viscous polymers formed a consistent hydrogel that could block the solvent's deeper penetration into the core of the HBS. The matrix integrity of these HBS capsules was satisfactory.

In vitro drug release studies were carried out in simulated gastric fluid (pH 1.2), as dissolution medium. All these HBS capsules containing aceclofenac showed sustained drug release over 5 hours (Figure 1). It was observed that the F-8 & F-2 formulations aceclofenac HBS capsule showed the highest and least amount of drug release throughout the specified time and release study revealed that the HPMC K4M was not sufficient enough to retard the drug release because this may due the fact that HPMC upon contact with water forms a hydrogel layer but aceclofenac release was greatly retarded by incorporation of carbopol 934 in HBS capsule .Carbopol 934 is a cross-linked polymer of acrylic acid with high molecular weight (~2 × 10^6 Da) and viscosity; when contacted with water, it swells and holds water inside its microgel network and also carbopol remain unionized in acidic medium which provide gel strength and integrity. This particular property may be accounted for its release retardant effect[25].

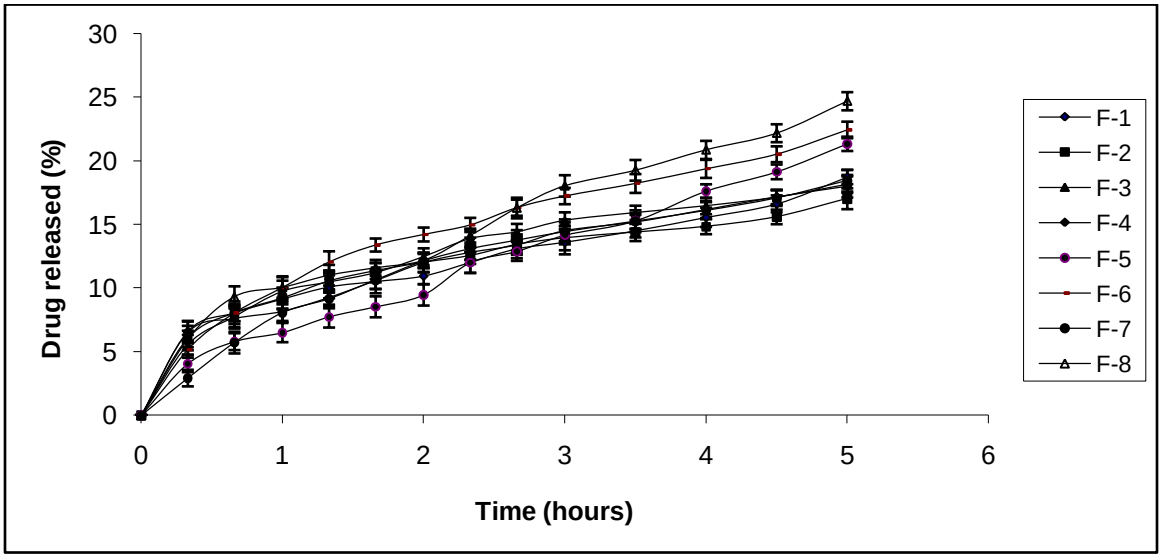

Figure 1: In vitro drug release from various HBS capsules containing aceclofenac in simulated gastric fluid, pH 1.2.

Again, Siepmann and Peppas suggested that the drug release from hydroxypropyl methylcellulose matrices is sequentially governed as follows [26]: (i) At the beginning, steep water concentration gradients are formed at the polymer/water interface resulting in water imbibition

into the matrix; (ii) Due to the imbibition of water, hydroxypropyl methylcellulose swells resulting in dramatic changes of polymer, drug concentrations and increasing dimensions of the system; (iii) Upon contact with water, the drug dissolves and diffuses out of the device due to concentration gradient; and (iv) With increasing water content, the diffusion coefficient of the drug increases substantially. Whereas, the drug release from these HBS capsules was increasing with the addition of pectin due to its hydrophilicity and low viscosity.

To analyze the mechanism of drug release from these aceclofenac HBS capsules, the *in vitro* dissolution data were fitted to various mathematical models like zero order, first order, Higuchi, and Korsmeyer-Peppas models. The results of the curve fitting into these above-mentioned mathematical models are given in Table 3. The drug release pattern of HBS capsules of formulation F-1, F-4, F-5 and F-8 were correlated well with first order model (R^2 = 0.9886, 0.9848, 0.9936 and 0.9857) over a period of 5 hours. Whereas F-2 to F-3 was correlated with Korsmeyer-Peppas model (R^2 = 0.9957 to 0.9938) over a period of 5 hours and F-6 to F-7 was correlated well with Higuchi model (R^2 = 0.9963 to 0.9877, respectively) when their respective correlation coefficients in simulated gastric fluids were compared.

Table 3: Results of curve fitting of the in vitro aceclofenac release data from different aceclofenac HBS capsules in simulated gastric fluid, pH 1.2.

Formulation code	Zero order		First order		Higuchi		Korsmeyar-Pepas	
	R^2	K_0 (Hour^1)	R^2	K_{1st} (Hour^1)	R^2	K_H (Hour^1)	R^2	K_P (Hour^1)
F-1	0.8833	0.0281	0.9886	0.0047	0.9655	0.0811	0.9695	0.0908
F-2	0.8165	0.0205	0.9447	0.0043	0.9438	0.0801	0.9957	0.0929
F-3	0.8374	0.0297	0.9412	0.0052	0.9792	0.0858	0.9938	0.0927
F-4	0.8942	0.0295	0.9848	0.0052	0.9846	0.0824	0.9696	0.0905
F-5	0.9831	0.0386	0.9936	0.0078	0.9407	0.0823	0.9706	0.0706
F-6	0.9055	0.0377	0.9656	0.0069	0.9963	0.0991	0.9927	0.0992
F-7	0.9074	0.0330	0.9384	0.0061	0.9877	0.0818	0.9706	0.0717
F-8	0.9473	0.0418	0.9857	0.0082	0.9742	0.0108	0.9605	0.1007

Here, the Korsmeyer-Peppas model has been also applied to analyze the *in vitro* drug release behavior of different pharmaceutical formulations to distinguish between various competing release mechanisms: Fickian release (diffusion-controlled release), non-Fickian release (anomalous transport), and case-II transport (swelling- controlled release). The value of release exponent (n) determined from *in vitro* aceclofenac release data of various HBS capsules ranged from 0.362 to 0.848 in simulated gastric fluid (Table 4), where F-1 to F-4 were followed the Fickian release (diffusion-controlled release) that could be attributed to the limited water uptake by these HBS capsules containing hydrocolloids. On the other hand, rest formulations were

followed the anomalous (non-Fickian) diffusion that might be high water uptake by these HBS capsules containing hydrocolloids leading to higher swelling of these capsules supported the anomalous release mechanism of aceclofenac.

Table 4: Release exponent and release mechanism of different aceclofenac HBS Capsules from *in vitro* drug release study.

Formulation code	Release exponent (n)	Release mechanism
F-1	0.367	Fickian
F-2	0.362	Fickian
F-3	0.430	Fickian
F-4	0.395	Fickian
F-5	0.848	Non- Fickian
F-6	0.513	Non- Fickian
F-7	0.633	Non- Fickian
F-8	0.498	Fickian

CONCLUSION

The various gastroretentive aceclofenac HBS capsules were prepared by using carbopol 934, HPMC K4M and pectin to control the delivery of aceclofenac for longer period of time in simulated gastric fluid. It was observed that the all these formulated HBS capsules were floated well over 5 hours with no floating lag time and showed sustained drug release in stomach environment at pH 1.2. The aceclofenac releases was found to be more sustain by addition of amount of carbopol along with hydroxyl propyl methyl cellulose in HBS capsule. The drug release pattern of these aceclofenac HBS capsules (F-1, F-4, F-5 and F-8) were correlated well with first order model where F-2 toF-3 and F-6 to F-7 was correlated well with Korsmeyer-Peppas model and Higuchi model. The results of current study clearly indicate a promising potential of these HBS capsules containing aceclofenac as an improved alternative to its sustained release dosage forms.

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