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Formulation and *in vitro* evaluation of an effervescent floating tablet of cefpodoxime proxetil prepared as an amorphous solid dispersion

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Abstract:

This study aimed to prepare an effervescent floating tablet to protect cefpodoxime proxetil (CP) from enzymatic hydrolysis and higher pH degradation in the lower parts of the gastrointestinal tract (GIT). CP was prepared as amorphous solid dispersion (ASD) with soluplus and Polyvinylpyrrolidone K30 (PVP K30) in a ratio of 1:1:1 by solvent evaporation technology.

Effervescent floating tablet formulations were prepared in different compositions and ratios by direct compression techniques using polyethylene oxide (PEO), hydroxypropyl methylcellulose K4M (HPMC K4M), sodium alginate (Na alginate) as a hydrophilic matrix, sodium bicarbonate (NaHCO₃), and citric acid as a gas-generating agent. These formulations were evaluated for floating ability and *in vitro* drug release. Then, an optimized tablet was performed to determine the hardness, friability, content uniformity, weight variation, and swelling index. The optimum formulation showed good buoyancy properties and extended drug release characteristics for 24 hours (hrs). The post-compression evaluation's parameters are within the limits of U.S. Pharmacopoeia. According to these results, the development of effervescent floating tablets of CP prepared as ASD could be effectively applied.

Keywords: amorphous solid dispersion, cefpodoxime proxetil, effervescent floating drug delivery system, and sustained release.

صياغة وتقييم قرص عائم فوار من سيفبودوكسيم بروكسيل مختبرياً محضر على شكل مشمت صلب غير متبلور

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الخلاصة

تهدف هذه الدراسة الى تحضير قرص عائم فوار لحماية سيفبودوكسيم بروكسيل من التحلل الانزيمي والتكسر في الاوساط القاعدية للأجزاء السفلية من الجهاز الهضمي. تم تحضير سيفبودوكسيم بروكسيل كمشتت صلب غير متبلور مع سولوبلس وبولي فنيل



بايريلدون بنسبة 1:1:1 بواسطة تقنية التبخر المذيبات. بعد ذلك تم تحضير عدة تركيبات من القرص العائم الفوار وبنسب مختلفة عن طريق تقنيات الضغط المباشر باستخدام أكسيد البولي إيثيلين، ألجينات الصوديوم وهيدروكسي بروبيل ميثيل سيليلوز كمصفوفات محبة للماء إضافة الى بيكربونات الصوديوم وحمض الستريك كعامل مولد للغاز. تم تقييم هذه التركيبات من حيث قدرتها على الطفو وتحرير الدواء في المختبر. بعد ذلك، تم اختيار القرص ذو أفضل نتائج لتقييم الصلابة والقابلية للتفتيت والمحتوى الدوائي وتباين الوزن ومؤشر الانتفاخ. أظهرت التركيبة المثالية خصائص طفو جيدة وخصائص إطلاق الدواء الممتدة لمدة 24 ساعة. تقع مقاييس تقييم ما بعد الضغط ضمن حدود دستور الأدوية الأمريكي. وفقا لهذه النتائج، يمكن تطبيق تطوير أقراص عائمة فوارة من سيفيدوكسيم بروكسيل المحضرة على شكل مشنت صلب غير متبلور بشكل فعال.

الكلمات المفتاحية: التشتت الصلب غير المتبلور، سيفيدوكسيم بروكسيتيل، نظام توصيل الدواء الفوار العائم، والتحرر المستدام.

INTRODUCTION

The oral drug administration is most favored because it is painless, has high patient compliance, is easy to manage, and is noninvasive [1, 2]. However, the primary obstacles to oral drug administration are poor absorption of certain medications and first-pass metabolism. Since absorption depends on the physicochemical properties, pharmaceutical and biological parameters of the drug and gastrointestinal tract (GIT) [3].

The physicochemical properties of drugs such as solubility, particle size, and crystallinity appear to have an influence on the processes of drug dissolution and absorption, as well as on their bioavailability. From a pharmaceutical perspective, the simplest dosage form is the solution that absorbed without needing extra processes. Other dosage forms must undergo disintegration, dissolution, and deaggregation to be absorbed in the GIT. While biological barriers include the pH sensitivity of drugs, which often refers to rapid degradation (changes in their structures or properties in response to a subtle shift in the pH in either acidic or basic media), and the eventual clearance of drugs through the GIT, which may occur before drug release. Moreover, the mucus layer covers the mucosal surface of the GIT, which forms a physical barrier for oral drugs, enzymatic hydrolysis, and liver metabolism [4-8].

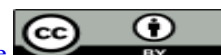
Gastroretentive drug delivery systems (GRDDS) are becoming increasingly prevalent because of their ability to regulate the time and site of drug release. Drugs that

unstable in the intestinal environment, have a narrow absorption window in the stomach or upper GIT, locally active in the stomach, and show poor solubility at high pH levels which is particularly interesting [9-13]. GRDDS may be achieved by mechanisms like mucoadhesion, superporous hydrogels, flotation, sedimentation, expansion, magnetic, and modified shape systems [14-21].

Davis was the first to describe the floating systems in detail in 1968. The density of these systems is less than that of gastric fluid (below 1.004 g/cm³) make them float on the stomach's surface. During this procedure, the medicine is gradually released at a defined rate to increase bioavailability, regulate plasma drug concentration fluctuations, and improve medication absorption. However, this system does not affect the gastric emptying. The residual system is emptied from the stomach depending on the gastric contents and the level of floating force [20, 22-24].

Among various approaches for GRDDS, only floating and swelling mechanisms have shown clinical evidence for prolonged gastric residence time at the fed state. Formulations of floating drug delivery systems that depend on buoyancy mechanisms are effervescent and non-effervescent systems. A gas-generating agent was present, and when the floating matrix tablet come into contact with the gastric media, carbon dioxide (CO₂) gas evolved as a result.

The hydration of the swellable polymer formed a gel that entangled and trapped CO₂, and



it was found that the density decreased less than the medium. As a result, the tablet bounced on the medium's surface. The evolution of CO₂ liberation from the tablet leaves pores that permit the drug release [20, 25-28]. Even with low density, the hydrophobic polymer did not swell or entrap the CO₂ generated, leading to the failure of the tablet floating [29].

Cefpodoxime proxetil (CP) is a broad-spectrum third-generation cephalosporin. It has been used most widely in treating skin infections, tonsillitis, pharyngitis, acute otitis media, respiratory tract infections, and sexually transmitted diseases [30]. CP is an orally administered prodrug that is absorbed and de-esterified by nonspecific Cholinesterase enzyme in the intestinal mucosa to release the active metabolite cefpodoxime [31, 32]. CP is a weak base with a molecular weight of 557.6 g/mole exhibiting a pH-dependent solubility, which is soluble in acidic solution but poorly in alkaline solution [33, 34]. Regardless of whether CP is synthesized to improve the permeability, it is still class IV; hence, absolute bioavailability is only 50% [35, 36]. The reasons for the low oral bioavailability of CP are mainly attributed to hydrolysis by pre-luminal choline esterase, typical gelation behavior in acidic environments, and low water solubility (400 µg/ml). Furthermore, it is prone to more degradation as it moves further to the lower parts of the GIT as a result of incline pH value [37-40]. Due to the short half-life of CP between 1.9 - 2.8 hours (hrs), the plasma levels dropped rapidly. For this reason, the drug is given twice daily. So, floating drug delivery system is required to achieve a constant plasma level of CP over 24 hrs [41, 42].

Merchant *et al.* mixed CP with hydroxypropyl methylcellulose 4000 cps (HPMC 4000 cps) to prepare a once-daily sustained-release tablet. *In vitro* dissolution studies were conducted in an acidic medium for the first 45 minutes and then for the rest

of the 24 hrs in phosphate buffer pH 6.8. HPMC 4000 cps effectively controls CP release for 24 hrs. However, they neglected to consider the enzymatic degradation in the lower GIT in their work [43]. While Sharma *et al.* formulated gastroretentive floating tablets using solid dispersion of CP with skimmed milk powder. Formulation containing solid dispersion, hydroxypropyl methylcellulose K4M (HPMC K4M), and xanthan gum in a ratio of 1:1.5:1 displayed a sustained release for just 12 hrs [44]. Kukati *et al.* prepared an effervescent floating tablet of CP with locust bean gum as a rate-control polymer in a 1:0.3 ratio. The optimum formulation showed a floating lag time of more than 13 min with 95% drug release in 0.1N HCL in only 12 hrs [45].

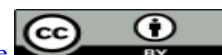
Among various polymer types, polyethylene oxide (PEO), HPMC K4M, and sodium alginate (Na alginate) are excellent polymeric excipients for preparing floating dosage forms owing to their nontoxicity, biocompatibility, low specific gravity, water-solubility, extended-release, and low production cost [46-49].

The present investigation's objective was to design and *in vitro* evaluate effervescent gastroretentive floating tablets of CP prepared as amorphous solid dispersion (ASD) with soluplus and Polyvinylpyrrolidone K30 (PVP K30) in a ratio of 1:1:1 for 24 hrs to overcome the enzymatic hydrolysis and high pH degradation in the lower part of GIT. Developed floating tablets were studied for post-compression parameters (hardness, thickness, and friability), floating evaluation, *in vitro* drug release profile, and swelling index.

METHODS

Materials

CP was supplied by the Hubei Widely Chemical Reagent Co., Ltd. (Wuhan, China).



soluplus supplied by BASF (Ludwigshafen, Germany). PVP K30 was obtained from CDH (P) Ltd. (Delhi, India). PEO is provided by micxy reagent Co., Ltd (Sichuan, China.). Na alginate, HPMC K4M, sodium bicarbonate (NaHCO_3), and Talc were supplied by HiMedia Laboratories Pvt. Ltd (Maharashtra, India). Citric acid was purchased from LOBA CHEMIE PVT. LTD. (Mumbai, India). Magnesium stearate (Mg stearate) was purchased from Alpha Chemika (Mumbai, India). All other chemicals were of analytical grade.

Preparation of an amorphous solid dispersion

First, the ASD of CP was prepared using the solvent evaporation method. CP, PVP K30, and Soluplus were accurately weighed in a 1:1:1 ratio and dissolved in methanol, followed by solvent evaporation technique using a rotary evaporator (Buchi Rotavapor R-205) from Switzerland. The dried film so obtained was passed through sieve no. 40 and further dried at 25 °C [50].

Differential scanning calorimetry (DSC)

Using DSC (Shimadzu, Japan), differential scanning calorimetry investigations were

carried out on CP and ASD. In tightly sealed aluminum pans, samples weighing 3-5 mg were heated at a rate of 10 °C/min between 30 and 200 °C [51].

Fourier Transforms Infrared spectroscopy (FTIR)

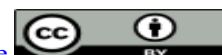
FTIR was carried out using an FTIR spectrometer (Shimadzu, Japan). The KBr disk technique was used to get the spectra of the CP, soluplus, PVP k30, and ASD formulation samples, with a scanning range of 400–4000 cm^{-1} [52].

Preparation of gastroretentive effervescent floating tablet

Direct compression was used to prepare the ASD (100 mg of CP) floating tablets by the formulation design displayed in **Table 1**. The ASD, polymer, NaHCO_3 , and citric acid were individually sieved through a 40-mesh screen. After that these ingredients were carefully weighed before being blended in a plastic bottle. Mg stearate and talc powder were then added. After that, the mixture was compressed into tablets using a minipress MII RIVA S.A. (Buenos Aires, Argentina) equipped with flat-faced punches (12 mm) [53].

Table 1: Composition of effervescent floating tablet formulations

Ingredients (mg)	formulation code							
	T1	T2	T3	T4	T5	T6	T7	T8
PEO	100	-	-	-	-	-	37.5	-
HPMC K4M	-	100	-	-	-	-	-	37.5
Na alginate	-	-	100	75	75	75	37.5	37.5
NaHCO_3	70	70	70	70	40	100	70	70
Citric acid	35	35	35	35	20	50	35	35
Lactose	25	25	25	50	95	5	50	50
ASD	300	300	300	300	300	300	300	300
Talc	10	10	10	10	10	10	10	10
Mg. stearate	10	10	10	10	10	10	10	10
Total weight	550	550	550	550	550	550	550	550



In vitro buoyancy study

The tablet's floating lag time (FLT) and total floating time (TFT) were used to evaluate its *in vitro* buoyancy. The test was performed by placing each tablet in a 500-mL beaker containing 0.1 N HCl with pH 1.2, maintained at 37 ± 0.5 °C for 24 hrs. A timing system visually measured the FLT and TFT.

Drug release study

The *in vitro* release study was conducted using 900 mL of 0.1 N HCl (pH 1.2) at

37 ± 0.5 °C with a rotation speed of 100 rpm using USP paddle apparatus II. At predetermined time intervals (1, 2, 3, 4, 6, 8, 10, 12, 14, and 24 hrs), aliquots of 5 mL were withdrawn and filtered through a 0.45 µm syringe filter. The withdrawn volume was replaced with fresh medium and analyzed using a UV spectrophotometer at 263.5 nm. The calibration curve equation of CP in 0.1 N HCl (pH 1.2) with correlation coefficient (R²) 0.9999 is:

$$Y = 0.0343X - 0.002 \dots\dots\dots \text{Equation (1)}$$

Post-compression evaluation of effervescent floating tablet**Tablet thickness**

Twenty randomly chosen tablets had their thicknesses measured with a vernier calliper.

Tablet hardness

Three tablets with known weights and thicknesses were tested, and the average crushing strength of each was recorded. A Monsanto hardness tester was used to gauge the tablets' hardness.

Weight variation

Twenty tablets were chosen randomly, and an electronic balance was used to calculate the average weight. Weighing each tablet separately, we compared its weight to the average.

Drug content

After weighing three tablets, they were placed in a mortar and milled into a fine powder. A 100 ml volumetric flask with 10 ml of methanol was filled with a precisely weighed amount of the powder. This solution was then diluted to 100 ml with 0.1N HCl. It was stirred for 1 hr. Then, it was filtered through a syringe filter of 0.45 µm. Absorbance was measured at 263.5 nm using a UV Spectrophotometer. The calibration curve equation (1) was utilized to calculate CP concentration.

Friability test

After precisely weighing twelve tablets (W1), they were put in a friabilitor and allowed to spin 100 times per four minutes. They were then reweighed (W2). The following equation was used to calculate the weight loss percentage:

$$\text{Friability (\%)} = (W1 - W2)/W1 \times 100 \dots\dots\dots \text{Equation (2)}$$

Swelling studies

The swelling behavior of the tablets was determined in triplicate. Briefly, the initial weight of tablets (W1) was measured and dipped in a beaker containing 900 mL of 0.1 N HCl using the basket. Tablets were

removed after regular time intervals (1, 2, 3, 4, 6, 8, 10, 12, 14 and 24 hrs) and weighed (W2) after removing the excessive medium from the surface [54]. This equation calculated the swelling index (SI):

$$SI (\%) = (W2 - W1)/W1 \times 100 \dots\dots\dots \text{Equation (3)}$$



Statistical Analysis

The data are presented as mean \pm standard deviation. One-way analysis of variance (ANOVA) was used to determine the statistical difference between different samples. The statistical analysis was conducted using Prism 8 software.

RESULTS AND DISSCUSION

Differential scanning calorimetry (DSC)

In **Figure1**, the DSC thermogram showed no sharp melting endotherm between 40 °C and 200 °C with Tg 99.69 °C, demonstrated the amorphous character of the CP.

Furthermore, absence of a sharp melting endotherm of ASD thermogram with a Tg of 94.58 °C clarified that the drug was still amorphous and miscible with the polymers.

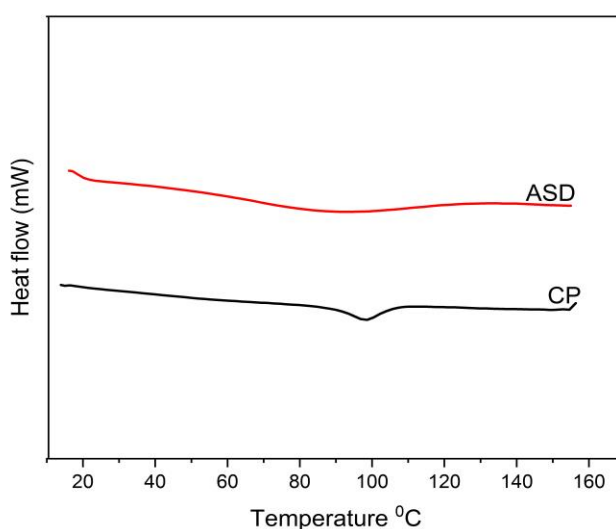


Figure 1: The DSC thermogram of CP and ASD (CP:soluplus:PVP 1:1:1)

Fourier Transforms Infrared spectroscopy (FTIR)

The interaction between the medication and the excipients is determined using FTIR. The ASD's FTIR spectrum revealed a number of notable variations compared to pure medication (**Figure 2**). Given that the peak associated with the N-H vibration at 3321 cm^{-1} of CP was considerably broadened and

shifted to a higher wavenumber at 3437 cm^{-1} . On the other hand, the pure drug's C-H vibration is significantly lower, shifting from 2985 cm^{-1} to 2978 cm^{-1} . In the meantime, the peak at 1759 cm^{-1} of CP that corresponded to the C=O stretching had a peak reduction and shifted to 1789 cm^{-1} . This suggests the formation of a strong hydrogen bond between the polymers and the CP.

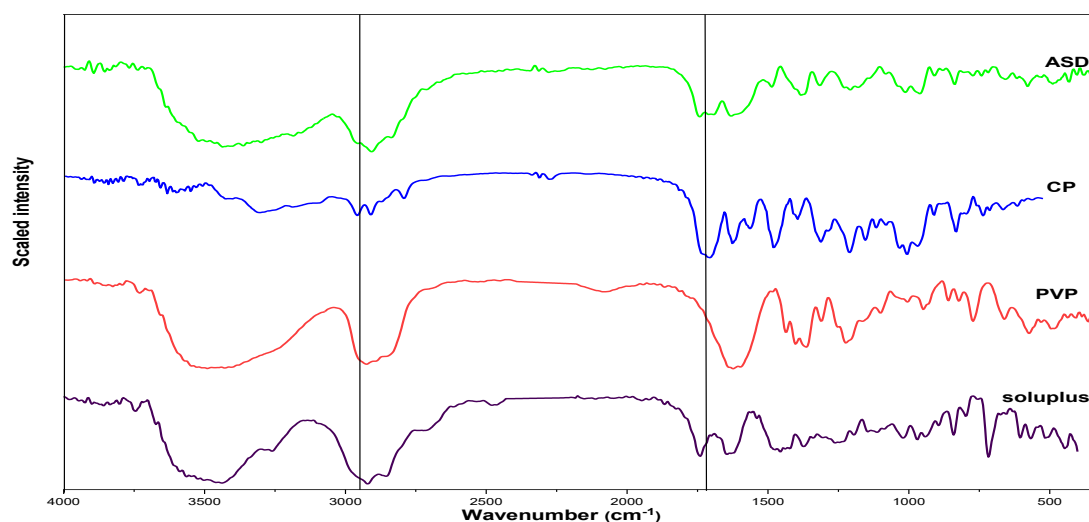


Figure 2: FTIR of soluplus, PVP K30, CP and ASD (CP:soluplus:PVP 1:1:1) formulation

In vitro buoyancy study

The time it takes for the formulation to start floating on the medium's surface is known as the FLT and the duration at which the tablet stays afloat after the lag period is known as the TFT. The longer the buoyant period and the shorter the lag time, the better, as in vivo, the faster FLT and longer TFT tablet is the less likely it is to empty from the stomach [55-57].

The results of *in vitro* buoyancy evaluation is included in **Table 2**. All tablets were

recorded with buoyancy lag time in the 1.31–10.54 min range and TFT of more than 24 hrs. T3 formulation containing only Na alginate had the shortest FLT. When the amount of Na alginate was reduced, the onset of the tablet floating was delayed, as in T4. Conversely, T2 exhibited a longer time to float than T1. Since HPMC K4M increases FLT more than PEO. Furthermore, preparing T7 and T8 by adding Na alginate to PEO and HPMC K4M individually in a 1:1 ratio accelerated the floating time [58].

Table 2: Evaluation of FLT and TFT of different effervescent floating tablets

Batch code	T1	T2	T3	T4	T5	T6	T7	T8
FLT (min)	8.52	10.54	1.31	1.76	8.02	2.17	2.9	2.55
TFT (hrs)	>24	>24	>24	>24	>24	>24	>24	>24

Table 2 depicts that FLT decreases in the presence of Na alginate in formulations. This effect could be explained by the point that Na alginate has a low density and high hydration rate, which leads to early gas entrapment that results in lesser FLT than HPMC K4M and PEO. Additionally, a decreased Na alginate concentration led to a thin gel layer, which

less entrapped the gas formed due to NaHCO_3 liberation, and the tablet floated slowly. Therefore, Na alginate was effectively minimized FLT. It could be observed that the quantity of gassing agents affects the tablet's FLT. T4 formulation with NaHCO_3 and citric acid 70 mg and 35 mg showed fast buoyancy, whereas lessening

their quantity, as in T5, slowed the tablet's floating. When the proportion of the effervescent mixture exceeded 70 mg and 35

mg, it had no significant influence on the tablet's buoyancy, as shown in T6 [59, 60].

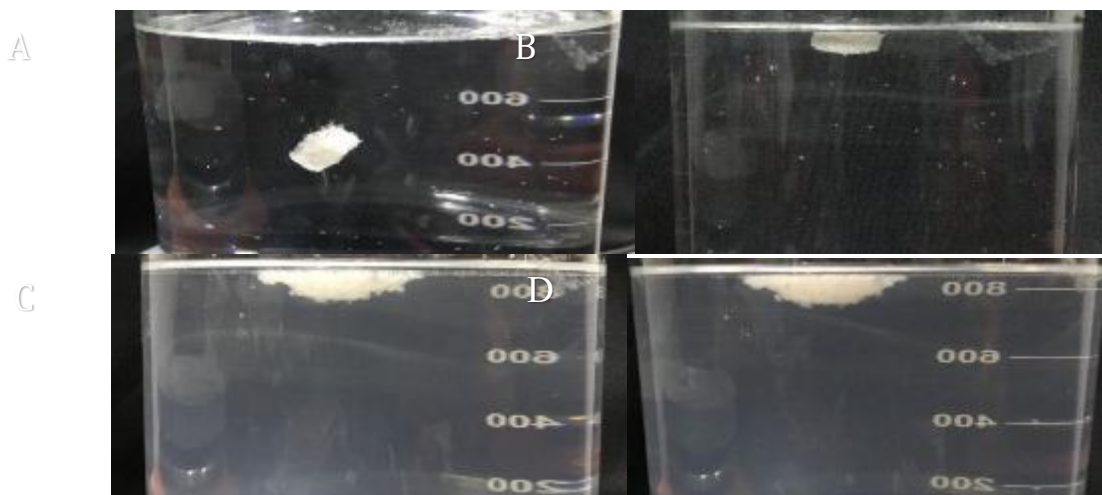


Figure 3: Photographs of *in vitro* floating behavior of optimized effervescent floating tablet formulation (T4) at A) 1.76 min B) 2 min C) 12 hrs D) 24 hrs

Drug release study

Preparing the gastroretentive formulation serves the primary goal of extending the time that CP is administered. Variable drug release profiles were successfully explored, depending on the type and concentration of the examined polymer(s) and the amount of gassing agent used in the current investigation.

Figure 4 displays the CP release from effervescent floating tablets. When T1 and T2 were formulated using PEO and HPMC K4M separately with ASD in a ratio of 1:3, less than 25% of the drug was released from their tablets within the first quarter of the test, and the drug concentration was around (69%, and 59%, respectively) after 24 hrs. The polymer has a higher viscosity in case of T1 and T2 that offers more excellent diffusional resistance through reducing the porosity of the tablet leading to a hindrance in drug release. While mixing Na alginate with ASD in a ratio of 1:3, about half of the drug quantity was released from T3 within 6 hrs,

and the drug release reached around 80% at the end of the experiment [61]. After reducing the Na alginate to ASD ratio to 1:4 as in T4, the release was accelerated, and the final drug concentration was elevated to approximately 91%. With decreasing amounts of polymer, the density of the swollen hydrogel network decreases, presenting less hindrance for drug diffusion. Consequently, the drug release rates increase and vice versa [62]. So, Na alginate significantly improved CP release (p -value < 0.05) compared with PEO and HPMC K4M.

In formulation T5, the amount of gassing agent was dropped. The release kinetics slightly increased, and the maximum drug release reached 93%. Whereby it was observed that as the concentration of gas-forming agent increased as in T6, this provided the fastest dissolution rate and nearly the same drug release percentage compared to T4 with a partial tablet erosion drawback after 5 hrs due to increased liberation of CO₂ that led to increased

porosity and the faster water penetration through the tablet matrix. Nevertheless, half a quantity of PEO and HPMC K4M was replaced with Na alginate separately as in T7

and T8; their dissolution rate inclined and the drug release about (77% and 68%, respectively) but they still less than T4.

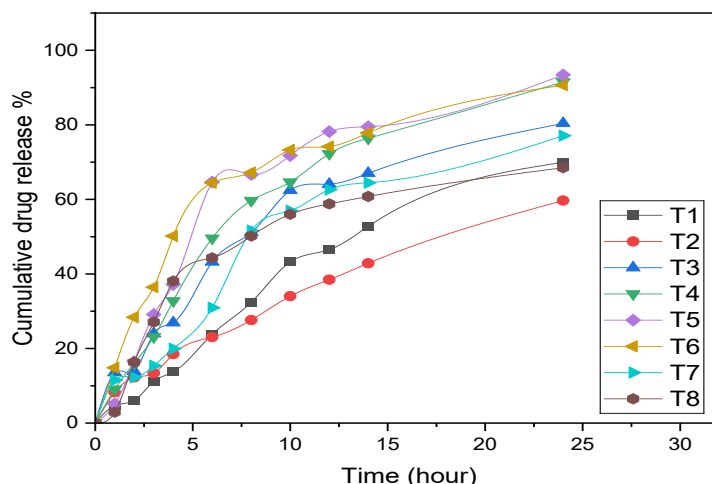


Figure 4: *In vitro* drug release profile of the effervescent floating tablets (mean \pm SD; n = 3)

Although the release rates of T4, T5, and T6 from the floating tablets were very similar, the selection of T4 is the optimum formulation based on T4 having FLT lower than T5. Additionally, T6 undergoes partial erosion within the first quarter of the release period.

Post-compression evaluation of effervescent floating tablet

Hardness is a determining factor in the tablet buoyancy and release. Variations in tablet hardness led to variations in density and porosity, altering the speed at which the dissolution media penetrates the tablet's surface, resulting in various drug release patterns. Therefore, tablets with lower

hardness had a shorter FLT and a quicker drug release, and vice versa. Additionally, lower hardness with high friability increases the signs of cracked, split, or broken tablets [29, 56, 63].

According to the results of the buoyancy study and drug release study, **Table 3** shows the physical characteristics of Formulation T4 as the model formulation. The formulations' hardness and thickness matched the requirements for acceptability. The weight variation and friability met the US Pharmacopoeia limits. Spectrophotometric analysis of the drug content revealed good content uniformity in the developed formulation.

Table 3: Post-compression parameters of effervescent floating tablet (T4) (mean \pm SD; n = 3)

Batch code	Thickness (mm)	Hardness (kg/cm ²)	Friability (%)	Weight variation (mg)	Drug content (mg/ml)
T4	5.98 \pm 0.012	4.13 \pm 0.2	0.78 \pm 0.13	550.66 \pm 1.69	101 \pm 1.63

Swelling studies

It is a gravimetric method that measures tablet water uptake (%) over time. This parameter is essential for determining the mechanism of drug release and is also responsible for floating behavior. **Figure 5** shows the percentage of swelling of T4 in 0.1 N HCl for 24 hrs. T4 had a swelling index of around 153% and readily absorbed water in only one hr. As immersion in the medium was prolonged, all records show a continuous

increase in swelling rate that reached about 368% after 6 hrs of the experiment. It is attributed to the high affinity of sodium alginate for the test media. This was well-matched to the results of Tadros *et al.* [64]. After that, the effect of the water flow caused the gel that had formed around the tablet to erode; the volume tended to stabilize and then eventually shrank [65].

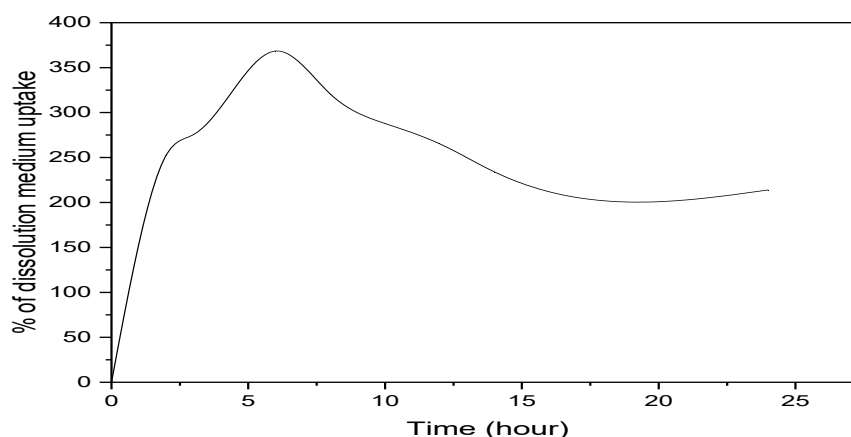


Figure 5: Percentage of medium uptake of effervescent floating tablet (T4) (mean \pm SD; n = 3)

CONCLUSION

An effervescent floating tablet of CP was formulated successfully. Tablets containing 75 mg of Na alginate as a retarding polymer demonstrated favorable *in vitro* characteristics. The optimized formulation T4 achieved a short FLT and sustained-release characteristic of 24 hrs. It will increase gastric residence time, which protects the drug from enzymatic and higher pH media degradation in the lower parts of GIT, which may further enhance the absorption and lead to improved bioavailability. Also, it will maintain plasma drug concentration, which inhibits bacterial resistance. Instead of administering a typical release product twice daily, the novel formulation, contained a 100 mg immediate-release tablet of CP offers an excellent alternative formulation dosage approach.

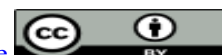
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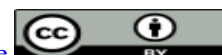
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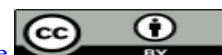
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