REVIEW ON FLOATING TABLET FOR ANTIVIRAL ACTIVITY OF ACYCLOVIR

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Abstract:

Advances in pharmaceutical science have significantly enhanced drug delivery methods through novel systems like NDDS, which introduce innovative ways to administer medications for better therapeutic outcomes.

Among various forms of non-digestible dietary supplements, liquid pills offer unique benefits tailored for diverse health requirements. Researchers developed pill-like substances suspended in water for better absorption of an antiviral medication into the bloodstream. A medication called acyclovir acts as an anti-virus agent; it's been utilized extensively over many years and can be administered via various routes such as orally, topically, or through injections. In clinical settings, this medication stands out as superior due to its advantages such as viral suppression prevention, safety profile, minimal adverse reactions, and affordability. Substances known as Floating Drug Delivery Systems (FDDS), which possess less dense properties compared to gastric fluid, remain suspended within it over extended periods while maintaining their rate of emptying into the small intestine unchanged. As it floats, the substance gradually dissolves and releases itself in an orderly manner through the pill. These portable pills aim to hasten the onset of medication effectiveness by initiating within minutes and sustaining therapeutic levels throughout an extended period of twelve hours. Additionally, these methods could potentially enhance absorption rates of the medication through efficient use and reduced dosing frequency requirements. A research project utilized ingredients such as hydroxy propyl methylcellulose K15M, polyvinylpyrrolidone K30, sodium bicarbonate, xanthan gum, guar gum, and microcrystalline cellulose for creating floatable tablet formulations. These devices utilized an advanced lab press equipped with multiple stations for performing rotational stamping operations on materials.

Key words: Acyclovir, Floating tablet, HPMC, PVP K30, Xanthan-Gum.

INTRODUCTION:-

The introduction states that gastro-retentive technologies enhance drug retention within the stomach for improved therapeutic efficacy by targeting medications specifically designed for their unique pharmacokinetic properties such as those requiring prolonged exposure due to an abnormally short absorption period, low aqueous solubility under acidic conditions typical of the ileum, or unstable formulations susceptible to degradation during transit through digestive organs like intestines and colon. This encompasses polymer-based adhesive formulations, inflatable structures, dense materials, suspended medication release devices (SMDRDs), highly permeable gels, and magnetically activated technologies. Acyclovir serves as an initial example of an anti-viral medication employed for treatment purposes. Different kinds of herpes diseases exist. Howard Schaffer subsequently found it together. Collaborate with Robert Vince, S. Bittner, and S. Gurwara regarding an adenosine derivative known as a cyclic adenosine, demonstrating significant antiviral efficacy. Subsequently, Schaffer collaborated with Burrow-Greene and expanded upon Acyclovir under the guidance of Pharmacist Gertrude Elion. A relatively brief duration in which drugs metabolize within organisms is characteristic for this substance. Five is equivalent to three in comparison. The three-hour period is

advantageous for creating sustained-release pharmaceuticals. In 1982, ACV, an FDA-approved synthetic purine nucleoside analog, became the world's first efficacious anti-viral agent; it has been widely utilized since then for treating numerous viral conditions such as HSV-1 & -2, VZV, EBV, and CMV across various bodily systems. Beginning since its inception in 1974, no recent antiviral medication surpasses acyclovir as effective against herpes simplex virus infections. These products can be found on the market as pills, chewable tablets, liquid medications taken orally, lotions applied topically, eyedrops administered directly into eyes, nose sprays used nasally, suppositories inserted vaginally, gel preparations rubbed onto skin, IV drips infused through veins, and powders mixed into fluids before being given by injection. Available under various trade names like Zovirax, Avirax, Virax, Civar, Lovir, and GenRx globally, at doses varying between 200 mg and 800 mg taken five times daily; dosage adjustments depend upon infection severity and individual patient response differences. A drug called acyclovir belongs to a class known as analogues derived from purines. It's primarily utilized in treating conditions like herpes viruses affecting types 1 and 2 along with varicella-zoster causing diseases including shingles and chicken pox. Studies indicate an approximate range for the absorption efficiency of acyclovir in the body at around fifteen percent up to thirty percent.

Acyclovir has a decay period of approximately one unit of time. Thirty minus two equals twenty-eight. Thirty hours post-oral intake, the medication demonstrates effective absorption within the duodenal region. Kharia's research involved creating an effervescent formulation for acyclovir through wet granulation techniques utilizing psyllium husks and HPMC K4M as matrices along with sodium bicarbonate as the gas generator to control release rates locally within the gastrointestinal tract, thereby improving oral efficacy. A research revealed that every formulation remained suspended during dissolving tests lasting longer than twenty-four hours. Another investigation conducted by Tavakoli et al demonstrated that tablet preparations incorporating hydroxypropyl methylcellulose potassium salt at up to thirty percent concentration along with sodium carboxymethyl cellulose ranging between thirty and forty percent, combined optionally with either two ten percent quantities of polyvinyl pyrrolidone or two fifteen percent amounts of sodium alginate, coupled with an effective gas-forming component maintained their buoyancy effectively under laboratory conditions. A new type of tablet was created for treating herpes infections through an innovative process called direct compression, where special materials like gelatin capsules and polyvinylpyrrolidone bind together in water-based solutions before being pressed into pills. Systems employing swelling polymers alongside effervent ingredients produce CO2 when mixed with stomach acids. Formulating an aqueous delivery system for acyclovir could enhance its intestinal uptake by prolonging the duration it remains within the stomach, thereby facilitating targeted distribution throughout the body at therapeutic levels.

Material and methods :

Acyclovir (Farabi Pharmaceutical Co., Iran, as a gift), metronidazole (Amin Pharmaceutical Co., Iran), Carbopol 934p (Colorcon, England), HPMC K4M, PVP, magnesium stearate, sodium bicarbonate, citric acid, methanol (HPLC grade), acetonitrile, isopropyl alcohol, dichloromethane, KH2PO4, triethylamine, and orthophosphoric acid (from Merck, Germany). All different chemical compounds and excipients had been analytical grade.

Preparation of floating formulations:

Floating tablets containing acyclovir were prepared by direct compression method. To prepare tablets, all ingredients (Table 1) were accurately weighed and screened through #18 sieve. The powders were mixed for 10 min using a cubic blender, then magnesium stearate was added as a lubricant and mixing was continued for another 2 min. The mixed powders were then compressed using an oval-shaped single punch tablet compression machine (GMBH-KS Kilian, Germany). The tablet punching machine was fitted with a 14 mm punch with a hardness of 60 N.

Formulations	Acyclovir	HPMC K4M	Cp934	PVP	$NaHCO_3$	Citric acid	FLT(min)	TFT (h)
H250G50	200	250	-	-	25	25	4.8 ± 0.26	23.7 ± 3.05
H175C75G50	200	175	75	-	25	25	0.8 ± 0.20	7.7 ± 1.53
H75C175G50	200	75	175	-	25	25	0.6 ± 0.10	20.3 ± 0.47
C250G50	200	-	250	-	25	25	17.1 ±	22.5 ± 2.25
H175P75G50	200	175	-	75	25	25	1.8 ± 0.31	16.8 ± 1.76
H125P100G75	200	125	-	100	37.5	37.5	0.3 ± 0.08	14.4 ± 0.80
H125P100G50	200	125	-	100	25	25	0.4 ± 0.12	14.8 ± 1.47

H and HPMC (Hydroxypropyl methylcellulose), C and Cp934 (Carbopol 934p), P and PVP (Polyvinylpyrollidone), G (gas forming agent), FLT (floating lag time), and TFT (total floating time).

Evaluation of blends before compression-

Hardness and malleability test:

The crushing strength of tablets was determined using a Monsanto type hardness tester (Rolex, Chandigarh, India). In all cases, the average of six replicate determinations was taken. Friability was determined by weighing 10 tablets after dusting, placing them in a fribilator (Rich-Rich Pharma, Bangalore, India) and rotating the plastic cylinder vertically for 100 revolutions[3]. After dusting, the total remaining weight of the tablet was recorded and the percentage (PF) was calculated using the formula PF= [(weight initial-weight final)/weight original]×100.

Uniformity of weight and drug content:

Weight uniformity was determined by wiping each tablet from dust and placing it in an electronic balance (Shimadzu BL-220H, Japan). The weight data of the tablets were analyzed for sample mean and percentage deviation. The uniformity of the drug content was determined by taking and powdering 5 tablets in a glass mortar, 100 mg of this powder was placed in a 100 ml stoppered conical flask. The drug was extracted with 0.1 N HCl and shaken vigorously on a mechanical gyratory shaker (100 rpm) for 5 h, filtered through cotton into a 50 ml volumetric flask and the filter was made up to the mark by flowing more 0.1 N HCl through the filter. Further appropriate dilutions were made and the absorbance was measured at 256 nm by UV/Vis double beam spectrophotometer (UV-1800, Shimadzu, Japan) using 0.1 N HCl as blank solution.

Carr's index

Carr's index was determined using the following formula:

$$Carr's\ Index\ (\%) = \frac{Tapped\ density - Bulk\ density}{Tapped\ density} \times 100 \quad (1)$$

Where, bulk density and tap density were determined by the cylinder method.

angle of repose (θ)

The angle of repose was determined by the funnel method using the following formula .

$$Tan\ \theta = \frac{h}{r} \quad (2)$$

Where, θ is the angle of repose, h is the height of the pile, and r is the radius of the pile.

Evaluation of floating tablet

Physical Properties of Floating Tablet

Tablet hardness, variation in weight, looseness, and uniformity of the contents of the floating tablets were determined by the procedure described in USP 35(10).

Floating interval time and total floating time

The floating lag time (FLT) and total floating time (TFT) of floating tablets were measured in a dissolution apparatus type II containing 100 mL 0.1 N HCl with the paddle rotated at 50 rpm (pH 1.2) at 37 ± 0.5 °C (11).

swelling index

The prepared tablets were placed in a glass containing 200 mL 0.1 N HCl at 37 ± 0.5°C. The percentage of swelling varies Kinetic analysis of dissolution data

To elucidate the drug release kinetics, the *in vitro* release data of different formulations were fitted to various kinetic models including zero order ($Q_t = Q_0 + K_0t$), First order ($\ln (Q_0-Q_t) = \ln Q_o + K_1t$), Higuchi ($Q_t = K_Ht^{0.5}$), Hixson-Crowell cube root law ($W_0^{1/3}-W^{1/3} = K_Ct$) and Korsmeyer Peppas model ($M_t / M_\infty = K\, t^n$).

In these model equations, Qt is the amount of drug released at time t, Q0 is the initial amount of drug in the pharmaceutical dosage form, t is the release time, Mt/M∞ is the fraction of drug released at time t, n is the diffusion coefficient for drug release that is dependent on the size of the matrix dosage form, K0 and K1 are rate constants, KH is the Higuchi dissociation constant, KC is the Hixon-Crowell dissociation constant, and K is the constant incorporating the surface-volume relationship. Based on the highest r2 value, the best fitting model was selected. n is the diffusion coefficient that reflects the mechanism of drug release. For cylindrical shaped tablets, $n \leq 0.45$ corresponds to the Fickian diffusion mechanism, $0.45 < n < 0.89$ belongs to non-Fickian release, $n = 0.89$ for Case II release, and $n > 0.89$ indicates super Case II release mechanism .

in vivo radiographic studies

X-ray stomach radiography was used to determine the gastric residence time of the tablets. The optimized floating tablet formulation (H125P100G75) was used for this purpose. The tablet must be opaque for X-ray examination, so 20 mg of the drug was replaced with barium sulphate (all other ingredients were kept constant). The amount of barium sulphate in the tablet should be sufficient to provide visibility by X-ray as well as maintain the ability to float. For in vivo assessment of gastric residence time, three healthy volunteers swallowed the tablet with a glass of water. Radiographic images of the tablets were recorded at intervals of 0.5, 1, 3 and 5 hours after ingestion of the tablets**.**

RESULT

Physical Properties of Powder

Carr's index and angle of repose were between 13.9 – 17.1 and 24.6 – 30.5 respectively, leading to good flow properties for the powder.

Physical characteristics of tablets

Acyclovir floating tablets showed uniform content (±3.4% variation) and reasonable friability (0.42 – 0.76%). The variation in weight of all seven formulations was within acceptable limits. Stiffness recorded at 60.5 – 69.8 N in vitro buoyancy study

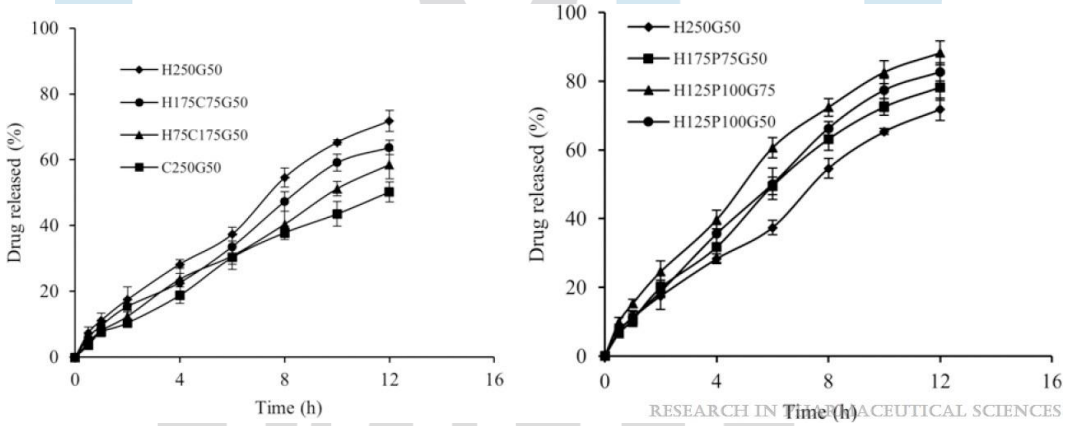
FLT and TFT ranged between 0.3 – 17.1 minutes and 7.7 – 23.7 hours, respectively (Table 1). With increase in gas forming agents, FLT decreased significantly. Inclusion of PVP in dosage forms significantly reduced FLT. In the optimized formulation (H125P100G75), FLT was approximately 18 s and remained active for 14.4 h.

swelling index

Addition of Carbopol 934P as a dosage form increased tablet swelling ($p < 0.05$). The inflammation index decreased with increasing concentrations of PVP ($p < 0.05$). Increased amount of gas forming agent in the formulation had no effect on the swelling index ($p > 0.05$).

in vitro drug release

The drug release profiles of acyclovir from formulations containing different amounts of excipients are shown in Figure 1. As shown in Figure 1, tablets containing HPMC K4M/PVP have appeared in earlier releases. Increasing the amount of Carbopol 934P decreased the drug release rate. As the concentration of PVP increased, the drug release rate increased. A direct correlation was observed between the tested concentration of gas forming agent and the drug release rate. Formulation H125P100G75 with the highest concentration of gas-forming agents showed the highest drug release rate .



Discussion

The objective of this study was to develop an optimized dosage form of acyclovir to achieve predictable sustained release floating tablets over 12 hours. Hydrophilic polymers including HPMC K4M and Carbopol 934p, which play an important role in floating tablets, were used to fabricate the floating tablet matrix. They are hydrated on contact with gastric fluids and form a low gravity matrix with buoyant properties, while active pharmaceutical ingredients were incorporated inside the matrix to create controlled release kinetics.

Carbon dioxide was produced when the floating tablets came in contact with acidic contents in the stomach. The gas generated was trapped inside the hydrophilic matrix causing the tablets to become buoyant. Increasing gas forming agents rapidly reduced the FLT by reducing the tablet density to 1 due to increased carbon dioxide release in the matrix. HPMC was the most important component to adjust the release profile of K4M acyclovir and buoyancy properties. This importance comes from the polymer's ability to rapidly produce a viscous gelatin layer, pH-independent hydration, and high capacity to load therapeutic agents. The swelling index depends on the polymer type and percentage that is used in the formulation. It was observed that the swelling index of the floating tablets increased with increasing concentration of Carbopol 934p. This indicates that Carbopol 934p retained more water than other polymers. This was in accordance with the study by Siddam et al. who observed an increase in the inflammation index as a result of increasing concentrations of Carbopol 934P.

CONCLUSION

Promising sustained-release floating tablets of acyclovir with gastroenteric potential were successfully prepared by effervescent technology using direct compression. Tablets containing 350 mg HPMC K4M, 50 mg PVP, 37.5 mg NaHCO3 and 37.5 mg citric acid showed desirable in vitro kinetic properties. The optimized formulation released the drug in a controlled manner and demonstrated a short buoyancy lag time with a total floating time of at least 14 hours. The gastro-retentive formulation developed in this study based on HPMC K4M and PVP polymer has good potential for sustained delivery of acyclovir in the management of viral infections.

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