INTERNATIONAL JOURNAL OF PHARMACEUTICAL RESEARCH AND NOVEL SCIENCES

IJPRNS

BIVARIENT TABLETS: A NOVEL APPROACH

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ABSTRACT

The Bi-varient tablet regimen is innovative drug delivery system. This is novel type of dosage form for oral administration in which one layer contains floating sustained release drug and another layer contains immediate release drug. This biCombination therapy has various advantages over mono therapy such as problem of dose dependent side effects minimized. A low-dose combination of two different agents reduces the dose-related risk; the addition of one agent may counteract some deleterious effects of the other. The term Bi-varient tablets refers to tablet containing subunits that may be either the same or different. Bi-varient tablets allow for designing and modulating the dissolution and release characteristics and they are prepared with one layer of drug for immediate release. Bi-varient tablets are preferred when the release profiles of the drugs are different from one another. While second layer designed to release drug latter, either as second dose or in an extended release manner.

Key words: Bivarient tablet regimen, biphasic release, floating sustained release

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INTRODUCTION

DRUG DELIVERY SYSTEM [1]

Every drug molecule needs a delivery system to carry the drug to the site of action upon administration to the patient.

Delivery of the drugs can be achieved using various types of dosage forms including tablets, capsules, creams, ointments, liquids, aerosols, injections etc. Most of these conventional drug delivery systems are known to provide immediate release drug without control over delivery rate.

A sustained release drug delivery system is a system in which a portion (the initial priming dose) of the drug is released immediately in order to achieve the desired therapeutic response promptly. The remaining dose of drug (the maintenance dose) is then released slowly there by resulting in a therapeutic drug/tissue level which is prolonged but not maintained constant.

Conventional release drug delivery system

A conventional oral dosage form is assumed to be one which is designed to release rapidly the complete dose of drug contained therein immediately following administration. In addition, the released drug is assumed to be in a form which is therapeutically available for absorption into the systemic circulation

Graphs which represent immediate and controlled release [2]

ISSN: 2395-0536

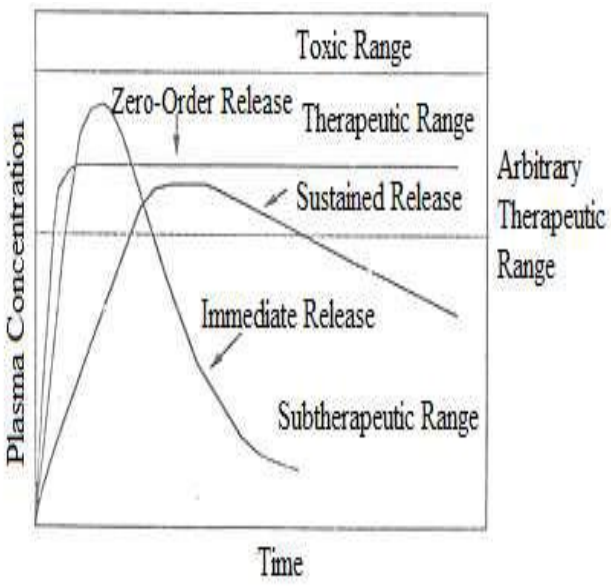

Fig:1 Graphs which represent immediate and controlled release

Mechanism of sustained release of drug [3]

On exposure to aqueous fluid, hydrophilic matrices take up water and polymer starts hydrating to form a gel layer.

Drug release is controlled by diffusion barriers or by surface erosion. An initial burst of soluble drug may occur due to surface leaching when a matrix containing a swellable glassy to a rubbery state which is associated with swelling process with time, water infiltrator deep into the case increasing the thickness by the gel layer. Concomitantly the outer layer becomes fully hydrated and states dissolving or eroding.

When water reaches the centre of the system and the concentration of drug falls below the solubility value, the release rate of drug begins to reduce. At the same time, an increase in thickness of the barrier layer with time increases the diffusion path length, reducing the rate of drug release.

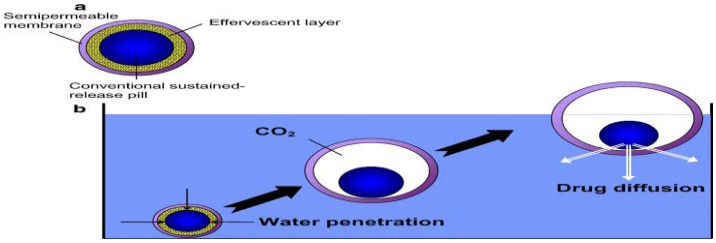

Fig: 2 Mechanism of sustained release of drug

Drug release kinetic associated with this layer dynamic range initially from fickian to anomalous and subsequently from quassi constant (near zero order) to constant.

In general, 2 major factors control the drug release from swelling controlled matrix system. They include

- The rate of aqueous medium infiltration into the matrix followed by a relaxation process (hydration, gelation or swelling).
- The rate of matrix erosion.

Advantages:

1. Maintenance of drug levels with a desired rate.
2. Reduced side effects.
3. Improved patient compliance.

Disadvantages:

1. Dose dumping.
2. Requirement of surgical procedures to implant or remove the system.
3. Higher manufacturing costs.

Difference between conventional and sustained drug delivery [4] TableNo.1 Difference between conventional and sustained drug delivery

Conventional drug delivery system	**Sustained drug delivery system**
High risk of toxicity	Very low risk of toxicity
Less patient compliance	Improves patient compliance
Not suitable for delivery of drugs with narrow absorption window in small intestine	Suitable for delivery of drugs with narrow absorption window in small intestine region
No risk of dose dumping	Possibility of dose dumping.
Not much advantageous for drugs a. having rapid absorption Through GIT. b. which degrade in colon c. acting locally in stomach d. which are poorly soluble at an alkaline pH	Very much advantageous for drugs a. acting locally in the Stomach. b. which degrade in the Colon. c. having rapid absorption through GIT.

Parameters for sustained drug delivery system [5]

1) **Desirable half-life** 3 - 4 Hours
2) **High therapeutic index** drugs with therapeutic index are unsuitable for incorporation in

controlled release formulation. If the system fails in the body, dose dumping may occur leading to fatalities.

3) **Small dose** if the dose of a drug in the conventional dosage form is high, its suitability as a candidate for controlled release is seriously undetermined. This is chiefly because the size of a unit dose controlled release formulation would become too big, to administer without difficulty.
4) **Desirable absorption and solubility characteristics**Absorption of poorly water soluble drug is often dissolution rate limited. Incorporating such compounds into controlled release formulations is therefore unrealistic and may reduce overall absorption efficiency.
5) **Desirable absorption window**Certain drugs when administered orally are absorbed only from a specific part of GIT. This part is referred to as the absorption window.

Drugs exhibiting an **absorption window** like fluorouracil, thiazide diuretics, if formulated as controlled release dosage form are unsuitable.

First pass clearance Delivery of the drug to the body in desired concentration is seriously hampered in case of drugs undergoing extensive hepatic first pass metabolism, when administered in controlled release forms.

BIVARIENT TABLETS

One of the novel approaches in the area of oral sustained release drug delivery is gastro retentive drug delivery system(GRDDS). Drugs that are having a narrow absorption window and having more solubility in gastric region are suitable candidates for GRDDS[6]. GRDDS prolongs the retention time of dosage forms in the stomach or upper GIT, as to improve solubility, bioavailability & the therapeutic efficacy of the drugs[7]. Several techniques have been proposed to increases the gastric residence time of dosage forms such as buoyancy or floating system [8].

The biphasic system is used mostly when maximum relief needs to be achieved quickly followed by sustained release phase. It also avoids repeated administration of drug. Coronary vasodilator, antihypertensive, antihistaminic, analgesic, antipyretics & anti allergic agents are mainly used for this system. The biphasic system may contain one or two drugs for immediate release & sustained release layer [9].

The Bi-varient tablet is innovative drug delivery system. This is novel type of dosage form for oral administration in which one layer contains sustained release drug and another layer contains immediate release drug. Combination therapy has various advantages over mono therapy such as problem of dose dependent side effects minimized. A low-dose combination of two different agents reduces the dose-related risk; the addition of one agent may counteract some deleterious effects of the other.

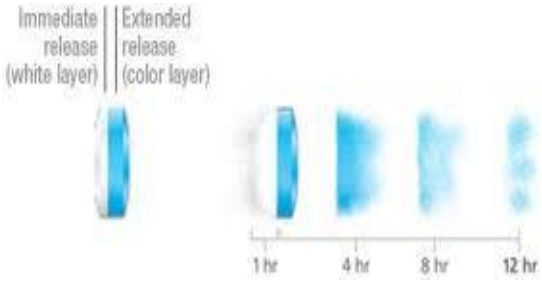

Fig: 3 Release of drugs from bivarient tablet

Using low dosage of two different agents minimizes the clinical and metabolic effects that occur with maximal dosage of individual component of the combined tablet and thus dosage of the single component can be reduced.

The term Bi-varient tablets refers to tablet containing subunits that may be either the same or different. Bi-varient tablets allow for designing and modulating the dissolution and release characteristics and they are prepared with one layer of drug for immediate release. Bi-varient tablets are preferred when the release profiles of the drugs are different from one another. While second layer designed to release drug latter, either as second dose or in an extended release manner[10].

The goal in designing sustained or controlled drug delivery system is to reduce the frequency of the dosing or to increase effectiveness of drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. So, controlled release dosage form is a dosage form that release one or more drugs continuously in a predetermined pattern for a fixed period time, either systemically or to a specified target organ. Sustained

release dosage forms, extends the life of the drug so that people shift from 3 times a day dosing to the new extende release tablets, taking them just once or twice a day [11].

FLOATING DRUG DELIVERY SYSTEMS

Floating drug delivery systems also called as hydrodyanamically balanced systems float on the gastric contents to release the drug slowly from the dosage form. The density of the FDDS should be less than the density of gastric fluid.

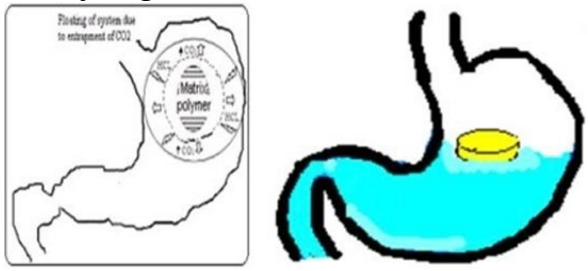

Fig: 4 Diagram of floating drug delivery system [12]

Advantages [13, 14]

- The gastro retentive systems are advantageous for drugs absorbed through the stomach. e.g: ferrous salts, antacids.
- Acidic substances like aspirin cause irritation on the stomach wall when come in contact with it. Hence HBS formulation may be useful for the administration of aspirin and other similar drugs.
- Administration of prolongs release floating dosage forms, tablet or capsules, will result in dissolution of the drug in the gastric fluid. They dissolve in the gastric fluid would be available for absorption in the small intestine after emptying of the stomach contents. It is therefore expected that a drug will be fully absorbed from floating dosage forms if it remains in the solution form even at the alkaline pH of the intestine.
- The gastro retentive systems are advantageous for drugs meant for local action in the stomach. e.g: antacids.
- When there is a vigorous intestinal movement and a short transit time as might occur in certain type of diarrhea, poor absorption is expected. Under such circumstances it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response.

Disadvantages:

- Floating system is not feasible for those drugs that have solubility or stability problem in G.I. tract.
- These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently-coat, water.
- The drugs that are significantly absorbed throughout gastrointestinal tract, which undergo significant first pass metabolism, are only desirable candidate.
- Some drugs present in the floating system causes irritation to gastric mucosa.

Applications of Floating Drug Delivery Systems

Floating drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability. These are summarized as follows.

1. Sustained Drug Delivery

HBS systems can remain in the stomach for long periods and hence can release the drug over a prolonged period of time. The problem of short gastric residence time encountered with an oral CR formulation hence can be overcome with these systems. These systems have a bulk density of <1 as a result of which they can float on the gastric contents. These systems are relatively large in size and passing from the pyloric opening is prohibited.

Eg: Sustained release floating capsules of nicardipine hydrochloride were developed and were evaluated *in vivo*. The formulation compared with commercially available MICARD capsules using rabbits. Plasma concentration time curves showed a longer duration for

administration (16 hours) in the sustained release floating capsules as compared with conventional MICARD capsules (8 hours) [15].

2. Site-Specific Drug Delivery

These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine, eg: riboflavin and furosemide. Eg. Furosemide is primarily absorbed from the stomach followed by the duodenum. It has been reported that a monolithic floating dosage form with prolonged gastric residence time was developed and the bioavailability was increased. AUC obtained with the floating tablets was approximately 1.8 times those of conventional furosemide tablets [16].

3. Absorption Enhancement

Drugs that have poor bioavailability because of site specific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption. Eg. A significantly increase in the bioavailability of floating dosage forms(42.9%) could be achieved as compared with commercially available LASIX tablets (33.4%) and enteric coated LASIX-long product (29.5%)[17].

Mechanism of floating drug Delivery system

Floating drug delivery systems have bulk density lesser than gastrtic fluids, so they remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system.

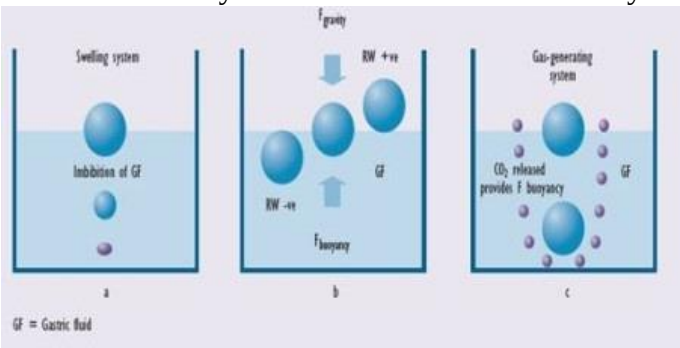

Fig: 5 Mechanism of Floating drug Delivery system

A minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface.

Floating force is determined by measuring continuously the force equivalent to F.

The tablet floats better if F is high. This floating force helps in optimising FDDS with respect to stability and durability of floating forces produced [18].

$$F = F_{buoyancy} - F_{gravity}$$
$$= (D_f - Ds)\, gv.$$

Where F = Floating force or total vertical force
D_f = Fluid density
D_s= Object density
V = Volume
g = Acceleration due to gravity.

Comparision of floating and non floating dosages

On comparison of floating and non floating dosage units, it was concluded that regardless of their sizes the floating dosage units remained buoyant on the gastric contents throughout their residence in the GIT, while the non floating dosage units sank and remained in the lower part of the stomach. Floating units away from the gastro duodenal junction were protected from the peristaltic waves during digestive phase while the non floating forms stayed close to the pylorus and were subjected to propelling and retropelling waves of digestive phase. It was observed that of the floating and nonfloating units, the floating units were had a longer gastric residence time.

Classification of floating systems[19]

(1) Single unit floating systems
   a. Effervescent system
   b. Non effervescent system

(2) Multiple unit floating system
   a. Effervescent systems
   b. Non effervescent systems
   c. Hollow microspheres

(3) Raft forming systems

EFFERVESCENT SYSTEMS

The concept of this system involves formation of carbon dioxide gas thereby causing reduction in density which makes the system easy to float in GI fluids.

The effervescent systems further classified into two types.

A. Gas generating systems

B. Volatile Liquid/Vacuum containing systems**.**

A. Gas generating systems

a) Intra gastric single layer floating tablets

These systems can be prepared by compressing the drug with gas (CO2) generating agents. These systems have low density than the GI fluid so that it can float for a prolonged period. The drug is released in controlled manner for a specified period of time.

b) Intra gastric bilayer floating tablets

These are also tablets which contain two layers, namely immediate release layer which is required to maintain the loading dose and sustained release layer which releases drug for sustained period.

c) Multiple unit type floating pills

These systems consist of effervescent agents inside and swelling membrane in outer layer. When it is placed in dissolution medium it swells, subsequently the density is reduced which makes it suitable for floating.

B. Volatile liquid containing systems

The concept involved in this system is sustaining the gastric retention by incorporating an inflatable chamber. This chamber contains a volatile liquid e.g. ether, cyclopentane, that gasifies at body temperature. The system also contains a bioerodible plug made up of PVA, polyethylene, etc.

a) Intragastric floating gastrointestinal drug delivery system

This system consists of a floatation chamber and microporous component. The floatation chamber is filled with gas and the drug is encapsulated in the microporous component.

b) Inflatable gastrointestinal delivery systems

This system contains two major compartments, one inflatable chamber which contains volatile liquid, and another drug compartment. After oral administration, the inflatable chamber inflates and holds the drug compartment in the stomach.

c) Intragastric osmotically controlled drug delivery system

This system consists of drug reservoir and osmogenic component. The mechanism involved in drug release is osmosis.

NON-EFFERVESCENT SYSTEMS

These system forms gel or swells when it contacts with gastric fluids. This is due to the presence of hydrocolloids. Due to the air entrapment in swollen matrix the density of this system becomes less than one, so that it floats.

The various types of this system are as:

a) Single Layer Floating Tablets

These tablets are prepared by mixing drug with a gel forming hydrocolloid which swells in contact with gastric fluid.

b) Bilayer Floating Tablets

These tablets contain two layers, one is immediate release layer which release drug for initial loading dose and another is bulk drug layer which release the drug in controlled manner throughout a period of time. This system absorbs in gastric fluid and forms gel which makes it to float.

c) Alginate beads

The formulation of alginate bead involves addition of sodium alginate solution to the aqueous solution of calcium chloride. This causes precipitation of calcium alginate. These beads are separated and then freeze dried to form porous system which can improve the gastric retention time.

Table No: 2 Commercial Floating Formulations [20, 21]

Name	Type and Drug	Remarks
MadoparHBS[â] (PropalHBS)	Floating capsule, Levodopa and benserazide	Floating CR capsules
Valrelease[â 34]	Floating capsule, Diazepam	Floating Capsules
Topalkan[â]	Floating Antacid, aluminum and magnesium mixture	Effervescent floating liquid alginate preparation

Conviron	Ferrous sulphate	Colloidal gel forming FDDS
Cifran OD[â]	Ciprofloxacine (1 gm)	Gas generating floating form
Cytotech[â]	Misoprostol (100 mcg/200 mcg)	Bilayer floating capsule
Liquid Gaviscone[â]	Mixture of alginate	Suppress gastro esophageal reflux and alleviate the heart burn

About polymer used

Hydrophilic cellulose polymers are commonly used as the excipient base in tablet systems. The effectiveness is based on the successive processes of hydration of the cellulosic polymer; gel formation on the polymer's surface; tablet erosion and the subsequent and continuous release of drug.

HPMC - A free flowing powder, a low density polymer, which is commonly used to provide the hydrophilic matrix. Tablets are prepared by thoroughly distributing HPMC in the formulation, preparing the granules by wet granulation or roller compaction and manufacturing the tablets by direct compression.

After ingestion, the tablet is wetted by gastric fluid and the polymer begins to hydrate. A gel layer forms around surface of the tablet and an initial quantity of drug is exposed and released. As water permeates further into the tablet the thickness of the gel layer is increased and soluble drug diffuses through the gel layer. As the outer layer becomes fully hydrated it erodes from the tablet core. If the drug is insoluble, it is released as such with the eroding gel layer. Thus the rate of drug release is controlled by the processes of diffusion and tablet erosion.

Types of HPMC

(1) HPMC K4m
(2) HPMC E50
(3) HPMC E15
(4) HPMC E5,9004-65-3
(5) HPMC K100

Applications

- Multipurpose additive.
- Thickner.
- Dispersant.
- Emulsifier.
- Film forming agent.

Evaluation of Floating Drug delivery system

- **A) Preformulation studies of granules**
- 1. Angle of Repose
- 2. Bulk Density
- 3. Tapped density
- 4. Hausner ratio
- 5. Carr index
- **B) Postformulation studies of floating tablets**
- 1**.** Weight variation
- 2. Hardness & friability
- 3. Buoyancy lag time & total floating time
- 4. Drug content
- 5. Drug release study.

FORMULATION OF BIVARIENT TABLETS

(a) **Formulation of immediate release granules**

Immediate reease granules were prepared by wet granulation method.

Procedure

1. Drug, dicalcium phosphate and cros povidone as super disintegrant was mixed properly in motar and pestle according to their compositions.
2. The resulting mixture or blend was passed through sieve #40.
3. To the above mixture, 10 % starch paste which is previously prepared was added slowly to make damp mass. The wet mass was passed through sieve # 60 and dried at 50^0C for suitable time. After drying the solid particles were passed through sieve # 40 with lubricants. Their granules were stored for further purpose.

   Note: The dye was mixed with binder solution.

(b) **Formulation of sustained release granules**

Granules were made by wet granulation method. All the ingriedients were drug, diluents, mixed thoroughly and the binding agent was added slowly to form cohesive mass. The damp mass was passed through sieve #60 and was dried at 50^0C for 45 min. Again the

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granules were passed through sieve no #40 and were mixed with lubricants. The granules were stored in well packed polythene cover for further purpose.

PHYSICAL EVALUATION OF GRANULES

The physical characteristics were studied individually for both granules before compression.

(a) Density measurement [22]

Generally two types of density were determined *i.e.*, bulk density and tapped density. The methods followed for calculation of the above two densities were determined by the following way

Bulk density

It is the ratio of total weight of powder to the bulk volume of powder. 10g of granules were weighed separately and transferred into a graduated measuring cylinder via a large funnel and measure the volume of the powder.

Bulk density = Weight of powder/ Bulk volume

(ii) Tapped density

It is the ratio of total weight of powder to the tapped volume of powder. After measuring the bulk density, tapped density was measured by tapping the powder for 500 times. Then the tapping was done for 750 times and the tapped volume was noted (the difference between bulk volume and tapped volumes should be less than 2%).

$$\text{Tapped density} = \frac{\text{weight of powder}}{\text{tapped volume}}$$

(b) Flow properties

(i) Hausner's ratio[23]

It is measurement of frictional resistance of the granules. The ideal range should be 1.2 – 1.5, Hausner's ratio is an important character to determine the flow property of powder and granules. This can be calculated by the following formula

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Value < 1.25 indicate good flow (=20% CI)

Value > 1.50 indicate poor flow (=35% CI)

(ii) Carr's index (Compressibility index)

The flowability of powder can be evaluated by comparing the bulk density and tapped density. It can be calculated from the following equation

$$\text{Carr's index} = \frac{(\text{Tapped density} - \text{bulk density}) \times 100}{\text{Tapped density}}$$

Table 3: Relationship b/w flowability and % compressibility

%compressibility	Flowability
5- 15	Excellent
12- 16	Good
18- 21	Fair-passible
23-35	Poor
33-38	Very poor
>40	Very very poor

(iii) Angle of repose

The angle of repose is defined as the maximum angle possible between the surface of piles of powder and the horizontal plane. Angle of repose of granules is done by fixed funnel method and is calculated by using following formula

$$\theta = \tan^{-1} h/r$$

where, h= height of the pile; r= radius of the pile the tangent of the angle is equal to the coefficient of friction(M) between the particles.

Table 4:Angle of repose as an indication of granule flow property[24]

S.No	Angle of repose	Type of flow
1	<25	Excellent
2	25-30	Good
3	30-40	Passable
4	>40	Very poor

Compression of bivarient tablet

Bivarient tablets were prepared using Rimek mini press (16 stations) machine. Bivarient tablets were compressed using 6mm oval shaped punches.

Bivarient tablet contains two layers i.e., immediate release layer and floating sustained release layer. Bivarient tablets were prepared by using optimized immediate and sustained release layer. Accurately weighed granules of immediate release blend and weighed granules of floating sustained release blend individually. Initially immediate release granules blend was fed manually into the die and then compressed at low compression force to form uniform layer. Subsequently floating sustained release layer granules blend was added to the die over that layer and completely compressed on tablet punching machine.

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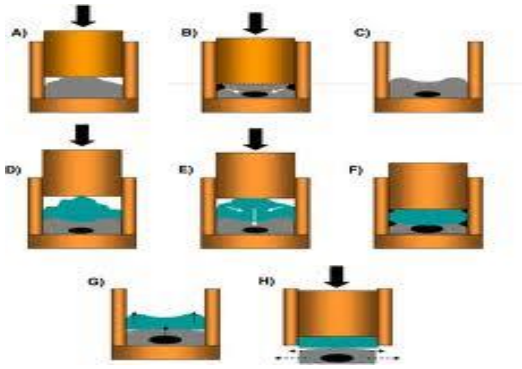

Fig 6: Steps involved in Bivarient tablet preparation

Steps involved in Bivarient tablet preparation:

- Filling immediate release granules into die.
- Slightly compressed immediate release granules.
- Ejection of upper punch.
- Addition of floating sustained release granules over immediate release granules.
- Compression of both sustained release granules and immediate release granules.
- Ejection of Bivarient tablet

CHARACTERIZATION OF BIVARIENT TABLETS

a. Physical Evaluation of tablets

Prepared Bivarient tablets were evaluated for hardness, friability, disintegration time for immediate release layer, drug content, percent drug release, weight variation, thickness, floating lag time and total floating time for floating sustained release layer.

I. Weight variation[25]

Randomly 20 tablets from each batch were taken for this study. Then the percentage deviation (as per IP ±5% for 500 mg tablet) of individual weights from the average weight and then standard deviation were calculated.

Table 5: Limits of weight variation as per USP

Average weight of tablet (Xmg)	Maximum % difference allowed
130 mg or less	10
130 mg to 324 mg	7.5
More than 324 mg	5

% maximum positive deviation = $(W_H - A/A) \times 100$

% minimum negative deviation = $(W_L - A/A) \times 100$

Where,

W_H = Highest weight in mg

W_L = Lowest weight in mg

A = Average weight of tablet in mg

II. Hardness

The resistance to the tablet chipping, abrasion or breakage under condition of storage, transportation and handling before usage depends upon its hardness. The hardness of tablets was determined by Monsanto hardness tester. The hardness should be within 1%. The hardness determinations are made throughout the tablet runs to determine the need for pressure adjustments on the tablet compression machine.

III. Friability

The friability of the tablets were determined by Roche friabilator. 20 numbers of tablets were weighed and placed in apparatus where they were exposed to rolling and repeated shocks resulting from freefalls with the apparatus. After a given number of rotations the tablets were weighed and the loss in weight indicates the ability of the tablet to withstand the type of wear. As per IP limit it should be <1%. The friability of the tablet was determined by the formula given below

Friability= $\frac{\text{Final weight – Initial weight}}{\text{Initial weight}} \times 100$

IV. Thickness[26]

The thickness of 10 randomly selected tablets from each batch was determined using digital Vernier callipers. The average thickness and standard deviation were calculated. Tablet thickness should have controlled within 5% variation of a standard value

V. *In vitro* Buoyancy Studies

The *in vitro* buoyancy was determined by floating lag time. The tablets were placed in a beaker containing 100ml 0.1N HCl and the time required for the tablet to rise to the surface and float was determined as floating lag time[27,28].

VI. Floating lag time & Total floating time [29]

The time taken for the tablet to rise to the surface and float was taken as floating lag time (FLT).

ISSN: 2395-0536

The duration of time the dosage form constantly remained on the surface of medium was determined as the total floating time (TFT).

VII. Assay

Randomly selected 10 tablets from each batch were powdered. Powder weight equivalent to 100mg of two drugs were dissolved in 100ml of distilled water and shaken vigorously for 10min. Dilutions were made to prepare 20µg/ml. Absorbance were taken by using UV- Vis spectrophotometer. The percentage of drug present in tablet

$$\%\text{Drug present} = \frac{\text{Sample}_{abs} \times \text{Std}_{dilution}}{\text{Std}_{abs} \times \text{Sample}_{dilution}} \times \text{Purity of Std} \times 100$$

***b. In vitro* Dissolution Studies (by UV method)**

The *in vitro* drug release study was performed using United States Pharmacopoeia (USP) XXII paddle apparatus [30].

Instrument: UV- spectrophotometer

Dissolution parameters

Medium : 0.1N HCl, Phosphate buffer pH 7.4
Volume : 900ml
Apparatus : USP XXII paddle type
RPM : 50
Time intervals: 30sec, 60sec, 90sec, 120sec, 1, 2,3,4,5,6,7,8 hrs.
Temperature: 37.0 ± 0.5^0 C.

Procedure

Phosphate buffer pH 7.4

27.218g of potassium dihydrogen phosphate was weighed into 1000ml of water and 0.8g of sodium hydroxide pellets are added to 1000ml of distilled water and adjusted the pH with sodium hydroxide pellets.

Sample preparation

One tablet was transferred into each dissolution bowls and the dissolution apparatus was runned as per dissolution parameters. 1ml of sample solution was withdrawn using micropipette. Replace aliquots withdrawn for analysis with equal volumes of dissolution medium which is maintained at 37.0 ± 0.5^0C and measured the absorbance at 272 and 273nm by using UV visible spectrophotometer and calculated the percentage drug release.

Table 6: Limits of *in vitro* dissolution studies for sustained release tablets [31]

Time (hrs)	Amount dissolved
2	NLT 25%
4	35-40%
8	50-60%
12	60-70%
18	80-90%
21	NLT 90%

Note: specifications regarding dissolution characteristics of **immediate release dosage forms** indicate that atleast 85% of the drug should be dissolved in a 60 minutes[32].

Kinetics of *in vitro* drug release[33]

To study the release kinetics *in vitro* drug release data was applied to kinetic models such as zero order, first order, Higuchi and Korsmeyer-peppas. To analyse the mechanism of the drug release rate kinetics o the dosage form, the data obtained were plotted as

1) Log cumulative percentage drug remaining Vs time(first order plots)
2) Cumulative percentage drug released Vs square root of time (Higuchi's plots)
3) Log percentage drug released Vs log time (Korsmeyer peppas).

Zero order

$$C = K_0 t \qquad (1)$$

Expressed in units of concentration/time and t is the time in h.

First order

$$\text{Log } C = \text{Log} C_0 K_t / 2.303 \qquad (2)$$

Where C is the concentration, C_0 is the initial concentration of drug, Kis the first order constant, and t is the time.

Higuchi

$$Q_t = Kt^{1/2} \qquad (3)$$

Where Q_t is the amount of the release drug in time t, K is the kinetic constant and t is the time in h.

Korsmeyer peppas

$$M_t / M_\infty = Kt^n \qquad (4)$$

where M_t represents amount of the released drug at time t,

M is the over all amount of the drug released after 8hrs

K is the diffusional characteristic of drug/polymer system constant and n is a diffusional or

release exponent that characterizes the mechanism of the drug release of drug.The value of n indicates the drug release mechanism related to the geometrical shape of the delivery system, if the exponent n=0.5, then the drug release mechanism is fickian diffusion. If n<0.5 the mechanism is quassi-fickian diffusion, and 0.5 < n < 1.0, then it is non fickian or anomalous diffusion and when n=1.0 mechanism is non fickian super case II[34].

Effect of stirring rate

The effect of stirring rate study was performed using United States Pharmacopoeia (USP) XXII paddle apparatus. The stirring rate study was performed using 900 ml of 0.1N HCl, at 37 ± 0.5 ^{0}C and 50, 75 and100 rpm. A sample (1ml) of the solution was withdrawn from the dissolution apparatus at specified time intervals and the samples were replaced with 1ml of fresh medium. The samples diluted to a suitable concentration with 0.1N HCl. Absorbance of these solutions was measured at 272-273 nm using a Shimadzu UV-1601 UV/Visible spectrophotometer. Cumulative percentage drug release was calculated using an equation obtained from a standard curve.

Short term stability studies

Stability of a drug can be defined as the time from the date of manufacture and the packaging of the formulation, until its chemical or biological activity is not less than a predetermined level of labelled potency and its physical characteristics have not changed appreciably or deleteriously. Stability studies were carried out as per ICH guidelines for tablets for a period of three months (at 40^0 C, RH 75%) using stability chamber (Indeecon company). The tablets were analyzed for weight variation, hardness, friability, buoyancy lag time, total floating time, buoyancy on distributing, drug content. Samples were assayed for percentage drug release once in a month for 3 months' time period.

Note: For stability studies reproducible batch of selected optimized formulation was used.

Table 7: Stability storage conditions

Study	Storage condition	Time period
Long term	25^0 C± 2 ^{0}C/60% RH±5%	12 months
Intermediate	30^0 C± 2 ^{0}C/60% RH±5%	6 months
Accelerated	40^0 C± 2 ^{0}C/60% RH±5%	6 months
Short term	40^0 C± 2 ^{0}C/75% RH±5%	3 months

Conclusion:

By this bivarient tablets the goal in designing sustained or controlled drug delivery system is to reduce the frequency of the dosing or to increase effectiveness of drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. Using low dosage of two different agents minimizes the clinical and metabolic effects that occur with maximal dosage of individual component of the combined tablet and thus dosage of the single component can be reduced. . A low-dose combination of two different agents reduces the dose-related risk; the addition of one agent may counteract some deleterious effects of the other.

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