



ISSN (E): 2277-7695

ISSN (P): 2349-8242

NAAS Rating: 5.23

TPI 2023; 12(1): 31-43

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www.thepharmajournal.com

Received: 05-11-2022

Accepted: 06-12-2022

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Optimization and evaluation of bilayer tablet of clonidine

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DOI: <https://doi.org/10.22271/tpi.2023.v12.i1a.18104>

Abstract

The goal in designing sustained or controlled delivery systems is to reduce the frequency of the dosing or to increase the effectiveness of the drug by localization the action, reducing the dose required or providing uniform drug delivery. The primary objective of sustained release drug delivery is to ensure safety and to improve the efficacy of drugs as well as patient compliance. Bi-layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose. The major objective of the work is the following: Clonidine is frequently administered up to 3 times in a day. So, the reducing dosing frequency by sustained release tablet, long term effect can be achieved by this dosage form, this drug help full in reducing high blood pressure and attention deficit hyperactivity disorder (ADHD), with the help of reduced fluctuation in plasma drug concentration, Reduction in side effect and dose related toxicity and patient compliance.

Keywords: Clonidine, bilayer, maintenance, ADHD, plasma

Introduction

Oral route has been the most widely used and most convenient route for the drug delivery. Oral route of administration has received more attention in the pharmaceutical industry and research field because of the flexibility in designing of dosage form and constraints like sterility and potential damage at the site of administration.

Approximately 50% of the drug delivery system available in the market is oral drug delivery system which has more advantages due to patient acceptance and easy to administration. The oral absorption of drug is often limited due to short GRT i.e. the time required for the content of the stomach to enter into small intestine.

Drugs that are easily absorbed from the GIT and have a short half-life are eliminated quickly from the blood circulation so they require frequent dosing. To avoid this drawback, the oral sustain/controlled release formulation have been developed in an attempt to release the drug slowly into the GIT and maintain the effective drug concentration in the serum for longer period of time.

All the pharmaceutical formulations for systemic effect *via* the oral route of administration must be developed within intrinsic characteristics of gastrointestinal physiology. The needs of GIT physiology, Pharmacodynamics, pharmacokinetics & formulation design is essential to achieve a systemic approach to the successful development of an oral formulation dosage form. The scientific framework required for the successful development of an oral drug delivery system consists of basic understanding of the following three aspects:

- Physicochemical, pharmacokinetic & pharmacodynamic characteristics of the drug.
- The Anatomical and physiological characteristics of GIT.
- Physicochemical characteristics & drug delivery system and type of dosage form design.

The manufacture of multilayer tablets has been successful for over 50 years and one of the early scientific evaluations of layered tablets was published by Stephenson (1961). New machine designs developed during the late 60s have made it possible to check the weight of individual layers by sampling without stopping the machine, providing in-process control facilities to ensure correct dosing, however, despite this, a considerable amount of expertise is still required to formulate these tablets and to ensure consistent manufacture to satisfy regulatory requirements.

One problem that causes great concern is the delamination of layered tablets which has become a more obvious problem with the increase in compression speed on modern high-speed rotary machines.

Tablet (Lachman., 1991) [18]

Tablet may be defined as a solid pharmaceutical dosage form containing a drug substance with or without suitable diluents and prepared by either compression or moulding method. They have been in widespread use since the later part of the 19th century and they are popularity continues. (Lachman., 1991) [18]

Advantages of tablet

1. Accuracy of dosage and ease of administration.
2. They are better suited to large scale production than other unit oral formulations.
3. They have chemical, mechanical and microbiological stability of all the oral formulations.
4. Convenience in packaging and dispensing.
5. Their cost is the lowest among all the oral dosage forms.
6. They are the lightest and the most compact amongst all the oral dosage forms.
7. They are easiest and cheapest for packaging and transportation.
8. They lend themselves to certain special release profile products such as enteric or delayed release products.
9. Tablets are better suited to large-scale production than other unit oral dosage forms.
10. They have the best-combined properties of chemical, mechanical, microbiological Stability amongst all the oral dosage forms.

Disadvantages of tablet

1. In case of elderly, children and the seriously ill patient may experience difficulties in swallowing the tablet.
2. Drug with low density characteristic, amorphous or flocculent nature, difficult to formulate as tablet dosage form because of resistance to compression.
3. Drug with bitter taste, objectionable odor or sensitive to oxygen or atmospheric moisture may require encapsulation or coating. In such case the capsule may offer the best and lowest cost approach.

Types of Tablets (Lachman., 1991) [18]

1. Tablets ingested orally

- Standard compressed tablets.
- Enteric coated tablets.
- Multiple compressed tablets.
 - Layered tablets.
 - Compression coated tablet.
- Repeat action tablet.
- Delayed-action and enteric coated tablet.
- Sugar and chocolate-coated tablet.
- Film-coated tablet.
- Chewable coated tablet.

2. Tablets used in the oral cavity

- Buccal tablets.
- Sublingual tablets.
- Troches and lozenges.
- Dental cones.

Tablets used to prepare the solution

- Effervescent tablets.
- Dispensing tablet.
- Hypodermic tablets.
- Tablets triturates.

Tablets administered by other routes

- Vaginal tablets.
- Implantation tablets.

Layer tablet

Layer tablets are composed of two or three layers of granulation compressed together. They have the appearance of a sandwich because the edges of each layer are exposed. This dosage form has the advantage of separating two incompatible substances with an inert barrier between them. It makes possible sustained-release preparations with the immediate-release quantity in one layer and the slow release portion in the second. A third layer with an intermediate release might be added. The weight of each layer can be accurately controlled, in contrast to putting one drug of a combination product in a sugar coating. Two-layer tablets require fewer materials than compression-coated tablets, weigh less, and may be thinner. Monogram and other distinctive markings may be impressed in the surfaces of the multilayer tablets. Coloring the separate layers provides many possibilities for unique tablet identity. Analytical work may be simplified by a separation of the layers prior to assay. Since there is no transfer to a second set of punches and dies, as with the dry-coating machine, odd shapes (such as triangles, squares and ovals) present no operating problems except for those common to keyed tooling.

Oral dosage forms such as tablets ("pharmaceutical powder compacts") are the most popular choice of administering drugs by both prescribers and patients alike. Oral dosage forms offer a quick and easy means of drug administration, and thus are highly suitable for aiding patient compliance in drug delivery for treatment of many diseases. In this respect, layered tablets have been suggested for controlled drug delivery.



Fig 1: Cross section of layer tablet

Multiple compressed tablets

These tablets are composed of at least two layers. Typically there are two designs of multiple compressed tablets:

1. Multiple-layered.
2. Compression coated.

In the former design, the first layer is formed by a relatively light compression of the drug containing powder mix/granules. The next layer is then formed by compression of the powder/granule mix (containing drug) on top of the lightly compressed first layer. Additional layers are formed in a similar fashion. In the second approach the initial layer is prepared by light compression (as described above), removed and located in a second tablet press. The granules/powders of the second coat are fed into the press and allowed to form a

constant mass around the surface (and edges) of the pressed tablet prior to compression to form the finished product. It is of course, possible to prepare tablets containing more than two layers although, in so doing, the complexity of the manufacturing process is dramatically increased. There are several applications for the use of multiple compressed tablets including:

The separation of drugs into separate layers that may be incompatible when formulated as a (single-layer) conventional tablet.

A multi-layered tablet is a tablet that has more than one individually compacted powder layer within its final single body. For example, a bi-layered tablet consists of two sequentially compact layers that form a single final coherent tablet body at the end of the compaction process. Multi-layered tablets are favoured due to their controlled release profiles of the active ingredient's dissolution profiles.

The delivery of therapeutic agents at different rates or to different sites within the gastrointestinal tract from a single tablet. The dissolution of the layers of the tablet or, indeed, the dissolution/diffusion of the drug from the layer may be controlled by the inclusion of polymeric excipients.

The production of coated tablets is important in cases where the drug has a bitter taste or where the drug is irritant to the stomach (e.g., non-steroidal anti-inflammatory drugs) or is chemically unstable under acidic conditions.

Tablet Manufacturing Methods

Tablets are manufactured by the following methods:

- Wet Granulation Method.
- Dry Granulation Method.
- Direct Compression Method.

Wet granulation method

The wet granulation method is the process in which a liquid is added to a powder in a vessel equipped with any type of agitation that will produce agglomeration or granules. These granules after drying are compressed to form tablets.

The unique portion of the wet granulation process involved the following steps

- Wet massing of the powder.
- Wet sizing or milling.
- Drying.

The liquid plays a key role in the granulation process. Liquid bridge is developed between the particles. Wet granulation is a popular technique within the pharmaceutical industry for the manufacture of tablets. There are several advantages and disadvantages associated with this technique.

Advantages of wet granulation

- Reduced segregation of formulation components during storage and/or processing, leading to reduced intra and inter batch variability.
- A useful technique for the manufacture of tablets containing low concentrations of therapeutic agents.
- Employs conventional excipients and therefore is not dependent on the inclusion of special grades of excipients (the requirement for spray-dried excipients in the direct compression method of tablet manufacture).
- Most manufacturing plants are built around wet granulation tablet manufacture.

Disadvantages of wet granulation

- Often several processing steps are required.
- Solvents are required in the process which leads to a number of concerns, e.g., the strength of this bond increases as the amount of liquid added is increased.

Dry granulation method

In this technique, there is no use of liquids. The process involves the formation of slugs and then the slugs are screened or milled to produce granules. The granules formed are then compressed to form tablets.

Advantages of dry granulation

- Both roller compaction and slugging require conventional (i.e. non-specialist) grades of excipients.
- These methods are not generally associated with alterations in drug morphology during processing.
- No heat or solvents are required.

Disadvantages of dry granulation

- Specialist equipment is required for granulation by roller compaction.
- Segregation of components may occur post mixing.
- There may be issues regarding powder flow.
- The final tablets produced by dry granulation tend to be softer than those produced by wet granulation, rendering them more difficult to process using post-tabletting techniques, e.g., film coating.
- Slugging and roller compaction leads to the generation of considerable dust. Therefore, containment measures are required. Furthermore, there may be a reduction in the yield of tablets.

Direct compression method

The process by which tablets are compressed directly from powder blends of the active ingredient and suitable excipients, which will flow uniformly in the die cavity and forms a firm compact.

Advantages of direct compression

- There are fewer processing steps (unit operations) and therefore the method is potentially more cost-effective than other methods.
- Direct compression does not require the use of water or other solvents. This, therefore, negates potential problems regarding the stability of therapeutic agents in the presence of the solvents. In addition, heating (a costly unit operation) is not required in direct compression.
- Lubrication is performed in the same vessel as powder mixing, thereby reducing both transfer losses and contamination of equipment.

Disadvantages of direct compression

- Specialist (and more expensive) excipients are required. The excipients that are used for direct compression processing are typically specially processed (e.g., spray-dried) for this application to achieve the correct physicochemical properties.
- The quality of the final dosage form is dependent on the powders being easily mixed and remaining homogeneously mixed. Segregation of the mixed components is minimized by ensuring that the excipients

and the dosage forms exhibit similar morphologies, densities and particle size/distribution properties.

- There may be issues regarding powder flow into the tableting machine.

Various techniques for bilayer tablet

OROS® push pull technology

This system consists of mainly two or three layers among which one or more layers are essential to the drug and the other layer are consist of push layer (Fig.1). The drug layer mainly consists of drug along with two or more different agents. So this drug layer comprises of drug which is in poorly soluble form. There is further addition of suspending agent and osmotic agent. A semi-permeable membrane surrounds the tablet core.

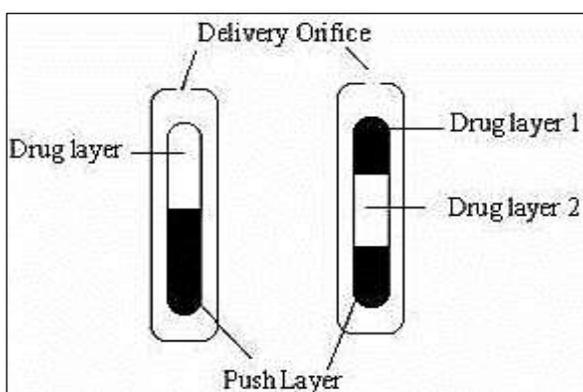


Fig 2: Bilayer and Trilayer OROS Push pull technology

L-OROS tm technology

This system used for the solubility issue Alza developed the L-OROS system where a lipid soft gel Product containing drug in a dissolved state is initially manufactured and then coated with a barrier membrane, than osmotic push layer and then a semipermeable membrane, drilled with an exit orifice (Fig. 2).

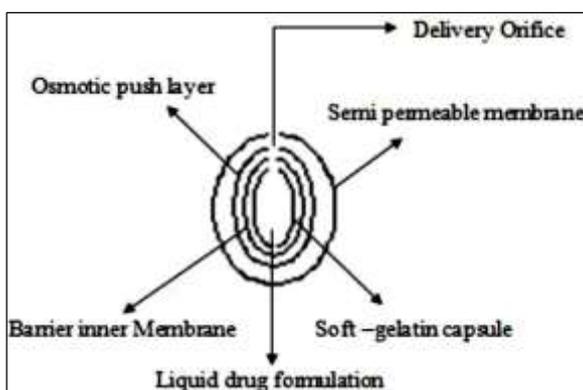


Fig 3: L-OROS tm technology

EN SO TROL technology

Solubility enhancement of an order of magnitude or to create optimized dosage form Shire laboratory use an integrated approach to drug delivery focusing on identification and incorporation of the identified enhancer into controlled release technologies.

DUROS technology

The system consists from an outer cylindrical titanium alloy

reservoir (Fig. 3). This reservoir has high impact strength and protects the drug molecules from enzymes. The DUROS technology is the miniature drug dispensing system that opposes a miniature syringe and religious minute quantity of concentrated form in continues and consistent from over months or Years.

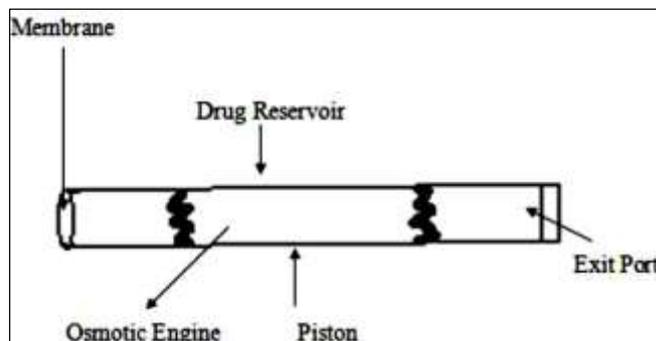


Fig 4: DUROS Technology

The DUREDAS™ system can easily be manipulated to allow incorporation of two controlled release formulations in the bi-layer. Two different release rates can be achieved from each side. In this way, greater prolongation of sustained release can be achieved. Typically, an immediate release granulate is first compressed followed by the addition of a controlled release element which is compressed onto the initial tablet. This gives the characteristic bi-layer effect to the final dosage form. A further extension of the DUREDAS™ technology is the production of controlled release combination dosage forms whereby two different drugs are incorporated into the different layers and drug release of each is controlled to maximize the therapeutic effect of the combination. Again, both immediate release and controlled release combinations of the two drugs are possible. A number of combination products utilizing this technology approach have been evaluated. The DUREDAS™ technology was initially employed in the development of a number of OTC controlled release analgesics. In this case a rapid release of analgesic is necessary for a fast onset of therapeutic effect. Hence one layer of the tablets is formulated as immediate releases granulate. By contrast, the second layer of the tablet, through use of hydrophilic polymers, releases drug in a controlled manner. The controlled release is due to a combination of diffusion and erosion through the hydrophilic polymer matrix.

Compression cycle for bilayer tablet

Bilayer tablets are composed of two layers of granulation compressed together. They have appearance of a sandwich because the edges of each layer are exposed. They have the appearance of a sandwich because the edges of each layer are exposed. Bi-layer tablets are prepared with one layer of drug for immediate release with second layer design to release drug, later, either as second dose or in an extended-release manner.

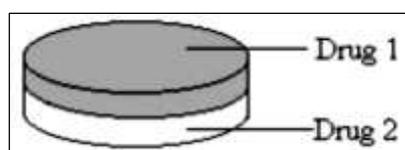


Fig 5: Bilayer Tablet

Bi-layer tablets are tablets, made by compressing two different granulations fed into a die succession, one on top of another, in layers. Each layer comes from a separate feed frame with individual weight control. Rotary tablet press can be set up for

two or three layers. More are possible but the design becomes very special. Figure represents compression cycle of bi-layer tablet.

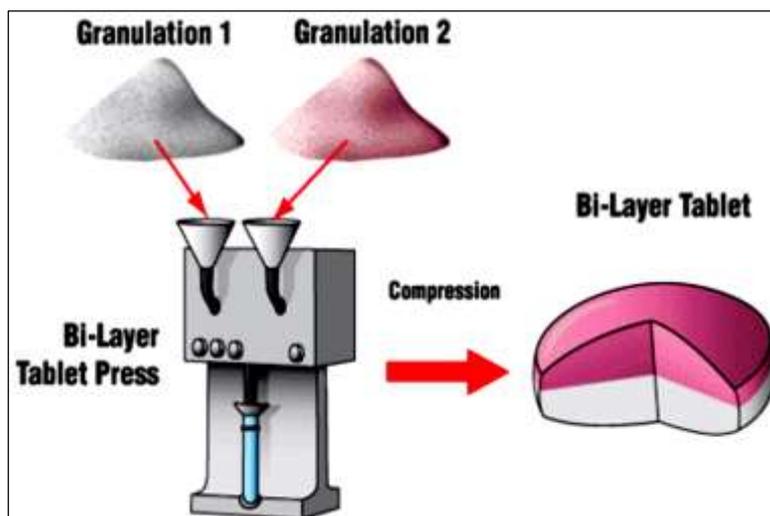


Fig 6: Bilayer tablet press

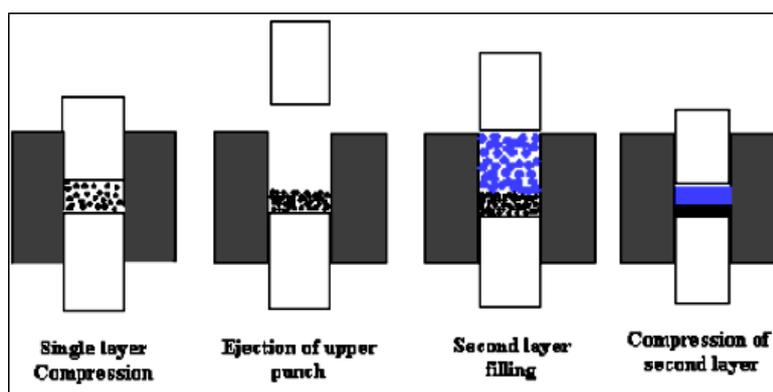


Fig 7: Compression cycle of Bilayer tablet

Compression force of bilayer tablet

Since the material in the die cavity is compressed twice to produce a bilayer tablet, compressed first with layer one followed by both the layers, the compression force affects the interfacial interaction and adhesion between the two layers. A certain amount of surface roughness of the initial layer is required for particle interlocking and adhesion with the second layer. As the surface roughness of the first layer is reduced, the contact area for the second layer is significantly reduced at the interface and makes the adhesion weaker. Immediately after final compaction, the compressed second layer may release the stored elastic energy unevenly and may produce crack on the first layer which could act as a stress concentrator and eventually make the tablet interface weaker. This may result in capping or de-lamination of the tablet along the interface either during manufacturing or immediately after the level of compression force used in the compaction determines the degree of roughness of the first layer. The higher the first layer compression forces the lesser the surface roughness resulting in reduced adhesion with the second layer. Therefore, for a given final compression force the strength of interfacial adhesion decreases with the increasing first-layer compression force.

Press design for quality bilayer tablets

Several pharmaceutical companies are currently developing Bilayer tablet for a variety of reasons: patent extension, therapeutic. To reduce capital investment quite often existing but modified tablet press are used to develop and produce such tablets. The development and production of quality Bilayer tablets need to be carried out on purpose-built tablet presses to overcome common Bilayer problems such as layer separation, insufficient hardness inaccurate individual layer weight control, cross contamination between layers, reduced yield etc. using a modified tablet press may therefore not be your best approach in producing a quality Bilayer tablet under GMP conditions. Especially when in addition high production output is required.

Ideal properties of bilayer tablet press

To produce a quality Bilayer tablet, in a validated and GMP-way it is important that the selected press is capable of

- Preventing capping and separation of the two individual layers that constitute the Bilayer tablet.
- Preventing cross contamination between the two layers.
- Producing a clear visual separation between the two layers and high yield.
- Accurate and individual weight control of the two layers.

Ro Tab Bilayer

- 1) Compactest bilayer rotary tablet press on the market with high sophisticated R&D and production functions.
- 2) Noise and vibration reduced for optimum operation in the lab.
- 3) Easy maintenance by automatically punch lubrication with interval setting.
- 4) Optimized for operation with only one occupied punch station.
- 5) Easy sampling for first layer (weight adjustment).
- 6) 2 Optifiller for 1st and 2nd tablet layer with special dust extraction rails to minimize cross-contamination.
- 7) A touch screen display allows operating and controlling the machine easily by the operator and visualizes all machine parameters, as compaction forces, speeds, tablet production etc.

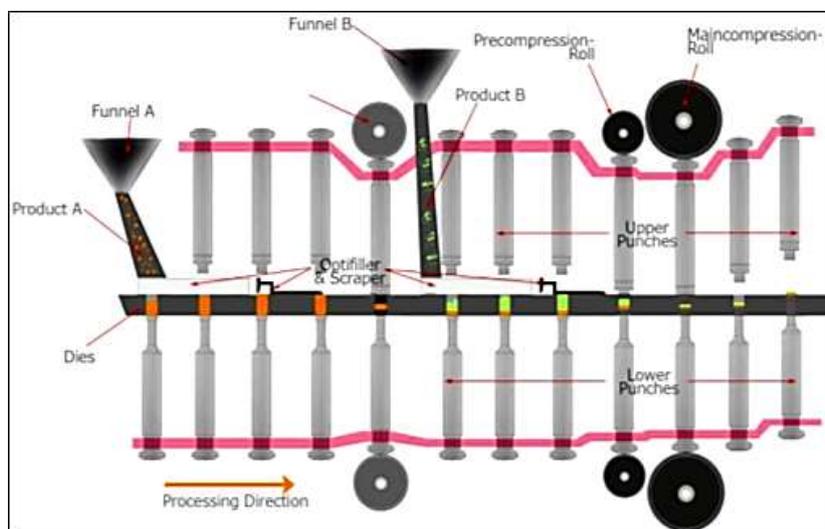


Fig 8: Ro Tab bilayer

Mini Bi-Layer Press (for compression of double layer tablet)

- 1) Designed to represent two-layer tablet productions at a small scale.
- 2) Larger turret diameter & variable speed allow for realistic scale up to large rotary presses.
- 3) Two forces feeder system helps to maintain uniform die fill and represents production equipment.
- 4) Pressure compensation hydraulic system.
- 5) Tablet thickness & weight adjustment settings are outside the machine.
- 6) Designed as per cGMP norms.
- 7) Lower punch seal to avoid jamming of the lower punches.
- 8) Transparent Guards at compression zone with safety switches.

KORSCH XM 12 Bi-Layer tablet press

It is a small-scale press that is ideal for product development, scale-up, clinical trials, and midrange production. The bi-layer execution, single-layer conversion kit, and exchangeable turret offer unprecedented flexibility. The XM 12 Bi-Layer Tablet Press offers a new standard in GMP with extreme accessibility to the compression zone and combinations of quick disconnects and smooth surfaces that permit fast cleaning and changeover. The XM 12 Bi-Layer Tablet Press features a retractable second layer feeder that permits automated first layer sampling at production speeds. The first layer sampling capability also offers a hardening feature, in which the main compression station will automatically compress the first layer tablet for in-process measurement. The two feeders are zero clearance and are configured with an integrated dust extraction manifold, which cleans the die table and completely eliminates any potential for cross-contamination.

MODUL™ P rotary tablet press with Bi-layer ECM

GEA Courtoy's MODUL™ P, the smallest tablet press in the MODUL™ range, is now available with an Exchangeable Compression Module (ECM) for bi-layer tablet (bilayer) production. The MODUL™ P with bi-layer ECM is the first press to enter the market that enables continuous bi-layer tableting on a small scale. It is the perfect solution to your bi-layer formulation development, clinical trial and other small-scale production needs.

Immediate release tablets

Immediate release tablets are designed to disintegrate and release the drug in the absence of any controlling features such as coatings or other formulation techniques. Despite a rising interest in controlled release drug delivery systems, the most common tablets are those intended to be swallowed whole disintegrating and releasing their medicaments rapidly in gastrointestinal tract.

A disintegrant is a substance in a tablet formulation that enables the tablet to break up into smaller fragments upon contact with gastrointestinal fluids. Such a rapid rupture of the tablet matrix increases the surface area of the tablet particles, thereby increasing the rate of absorption of the active ingredients and producing desired therapeutic action. The proper choice of disintegrants and its consistency of performance are critical to formulation development of immediate release tablets. In the past starch was one of the most widely used inexpensive and effective tablets disintegrant. A high concentration of starch is required to bring about effective disintegration. Scientists' search for disintegrating agents with efficient disintegrating properties at relatively low concentrations has led to the development of new compounds with excellent disintegrating properties.

Super disintegrant: Generally used at a low level in the solid dosage form, typically 1-10% by weight relative to the total weight of the dosage unit.

Table 1: list of super disintegrant

S. No.	Name	Brand Name	Manufacturer
1.	Cros povidone	Kolloidon, Polyplasdon XL	BASF, ISP'S
2.	Cross carmellose	Ac-Di-Sol	FMC Bio polymer
3.	Sodium Starch glycolate	primo gel	DMV international

Controlled drug delivery system

A controlled release formulation may increase the efficacy of compound and it may improve the patient compliance as the dosing frequency is reduced. Controlled release dosage form is the dosage form that releases one or more drug in a predetermined pattern for the fixed period of time either systemically or to a specified target organ.

The objective of controlled release technology is to minimize the time and concentration of active drug that is above or below the therapeutic window, while extending the duration of existence of the active agent within the efficacious range of concentration. It reduces the frequency of dosing, increases the effectiveness of drug by localization at the site of action, reduces the dose required and provides uniform drug delivery.

Delayed release

Delayed release systems are those that use repetitive intermittent dosing of a drug from one or more immediate release units incorporated into single unit dosage forms. These systems include the drug delivery systems that achieve slow release over an extended period of time. The drug is released at a time rather than immediately after administration i.e. the site of release is controlled.

Extended release

In the extended-release dosage form the drug is released slowly than normal manner at predetermined rate reduces the dosage frequency by two folds.

Site specific and receptor targeting

Site specific system refers to targeting of a drug directly to certain biological location. In this case the target is adjacent to or in the diseased organ or tissue. In receptor targeting the particular receptor for the drug with in an organ or tissue targeting of drug delivery directly to a certain biological location.

Advantages of sustained drug delivery system

- The frequency of drug administration is reduced.
- Patient compliance can be improved.
- Drug administration can be made more convenient as well
- The blood level oscillation characteristic of multiple dosing of conventional dosage forms is reduced.
- Better control of drug absorption can be attained, since the high blood level peaks that may be observed after administration of a dose of a high availability drug can be reduced.
- The characteristic blood level variations due to multiple dosing of conventional dosage forms can be reduced.
- Safety margins of high potency drugs can be increased

and the incidence of both local and systemic adverse side effects can be reduced in sensitive patients.

Factors affecting controlled drug release formulation

The purpose of designing controlled drug delivery system is to control the rate of delivery, controlling the duration of therapeutic activity and targeting and delivery of drug to tissue. The type of delivery system and the route of administration of the drug in controlled release form depend upon the following characteristics of the drug.

- **Molecular weight of the drug:** The drug with lower molecular weight undergoes faster and more complete absorption. Drug with larger molecular weight is poor candidate for controlled release system. eg proteins and peptides.
- **Aqueous solubility of drug:** A drug with good aqueous solubility especially if pH dependent serves as good candidate for controlled release dosage form e.g., pentoxiphyllin. Poorly soluble drugs are poor candidates for controlled release systems.
- **Apparent partition coefficient of the drug:** Drugs that have high partition coefficient are more suitable candidate for controlled release system.
- **Drug stability:** Drugs that are unstable in gastrointestinal environment cannot be administered as oral controlled release formulations e.g. Nitroglycerine.
- **Mechanism and site of absorption:** To maintain a constant blood or tissue level of drug it must be uniformly released from the controlled release product and then uniformly absorbed. Drugs absorbed by carrier-mediated transport processes are poor candidate for controlled release system.
- **Route of administration:** For controlled release oral formulation, the drug must get absorbed through the entire length of gastrointestinal tract. The transit time of the drug by this route is extended for 12 to 24 hrs. A drug whose absorption is PH dependent is poor candidate for controlled release formulation.
- **Absorption rate of the drug:** A drug with slow absorption is a poor candidate for controlled release formulation e.g., irons. Aqueous soluble but poorly soluble potent drugs like decamethonium are also unsuitable candidate since a slight variation in the absorption may precipitate potential toxicity.
- **Elimination Half-life:** Drugs with half-life of the range of 2-4 hours are good candidate for such system e.g., propranol, metoprolol, Dicloxacillin sodium. Drugs with long half-life need not be presented in such system.
- **Plasma concentration-response relationship:** Drugs whose pharmacologic activity is independent of its concentration are poor candidate for controlled release system e.g., reserpine.
- **Dose size:** Drugs with single oral dose larger than 0.5 gram are poor candidate for oral controlled products. Large dose will generate a substantial volume depending on the density of the drug, duration of intended prolongation and mechanism of absorption. The problem of large dose can be overcome by selecting an alternative route of drug administration.

Materials and Methods

Materials

Table 2: List of Materials

Material	Supplier
Clonidine	Srijan Pharma Pvt. Ltd, Indore
Hydroxypropyl Methyl Cellulose	SOP, Indore
Microcrystalline Cellulose	SOP, Indore
Magnesium Stearate	SOP, Indore
TALC	SOP, Indore

Table 3: List of Instrument

Instrument	Manufacturer
Electronic balance	Sartorius, U.K
Hot air oven	Lawrence and Mayo Pvt Ltd.
UV Spectrophotometer	Shimadzu-1800, Japan.
FTIR Spectrophotometer	Thermo Nicolet, Japan.
Sonicator	Enertech Electronics Pvt., ltd.
Tablet dissolution testing apparatus	Electro lab.
Rimek mini tablet press II	Karnavati Engineering Pvt. Ltd.
Monsanto and Pfizer hardness tester	Secor India.
Tablet friability taster	Roche friabilator.
Rotary flask shaker	Secor India.

Methods

Preformulation studies

- Organoleptic characteristics-colour, odour, appearance.
- Solubility.

A Qualitative determination was done by adding a solvent with small incremental amount to a test tube containing fixed quantity of solute (drug) or vice versa. After each addition, the system was vigorously shaken and visually observed. Solubility Profile of Clonidine in various solvents

Loss on drying

The Loss on Drying Test is a method to measure the loss in mass of the sample, when dried under the conditions specified in each monograph. The method is applied to determine the amount of the water all or part of water of crystallization, or volatile matter in the sample, which is removed during the drying.

Melting point

The pharmacopoeias regard the capillary method as the standard technique for melting point determination. According to this for melting point determination of the drug sample, small quantity of powder was placed into a fusion tube. That tube was placed in the melting point determining apparatus containing castor oil. The temperature of the castor oil was gradually increased automatically and temperature at which powder started to melt was recorded and the temperature when all the powder gets melted was also recorded.

Identification of drug by Infrared spectroscopy

Infrared spectroscopy is widely used analytical technique which provides information about the structure of molecule. Infrared spectrum of chemical substances is fingerprint for its identification. An infrared spectrum of drug was taken using KBr pellets. Small quantity of drug was mixed with oil and one drop was placed between KBr pellets. The pellets were in holder and infrared spectrum was interpreted for presence of different group in the structure of drug. The Fourier transform infrared spectra of showed Clonidine all characteristic peaks

of Clonidine

Bulk density

The bulk density of a powder is calculated using Equation given below and is the mass of the powder divided by the volume that the powder occupies.

$$\text{Bulk density} = \frac{\text{weight of the powder (g)}}{\text{Volume of the powder (ml)}}$$

Tapped density

The tapped density of a powder, calculated using below equation, is the ratio of the total mass of a powder to the volume occupied by that powder after it has been compacted or tapped for a specific period of time. Tapping the powder removes small voids or air entrapped between the particles in a powder blend. The tapped density is used to calculate the Hausner ratio (HR) that also provides an indication of the flow properties of a powder

$$\text{Tapped Density} = \frac{\text{weight of the powder (g)}}{\text{Volume of powder after being tapped (ml)}}$$

Angle of repose

In order to determine the AOR of a powder the material is poured onto a flat surface where it forms a heap. The particles initially stack, until the angle available for the addition of subsequent particles to the heap is large enough to overcome friction and the particles will slide down the surface of the heap until the gravitational forces balance the inter-particulate forces, and movement ceases. The heap of particles tends to form a conical shape with the sides of the heap producing an angle between the surface on which the powder resides and the free surface of the powder known as the angle of repose, which is indicative of the cohesion between particles and therefore an indirect measure of powder flow ability. The guidelines for AOR are summarized in Table below with values of < 25 being the most desirable and indicative of good flow properties

Partition coefficient

Partition coefficient was determined by the following procedure. 10 µg/ml solution of pure drug in water was prepared. Then the mixture of octanol and water were mixed in ratio of 1:1. Then this mixture was shaken properly for 30 minutes further the mixture was allowed to stand for one hour.

- Fourier Transform Infra-red spectroscopy

Results and Discussion

Results

Table 4: Physical properties of Clonidine

S. No.	Parameter	Observation
1.	Bulk density (g/cm ³)	0.704 ± 0.04
2.	Tapped density (g/cm ³)	0.847 ± 0.05
3.	Angle of repose (θ)	32°.07' ± 0.20
4.	Carr's index (%)	18 ± 0.40
5.	Hausner's ratio	1.20 ± 0.05

Table 5: Solubility profile of drug

S. No.	Solvent	Solubility
1.	Water	Sparingly soluble
2.	Phosphate buffer 5.8	Soluble
3.	methanol	Soluble
4.	0.1N HCl	Soluble

Table 6: Melting point of drug

Material	Specified	Observations
Clonidine	205 °C -210 °C	204 °C -207 °C

Table 7: Loss on drying

S. No.	Specification	Observation
1	NMT 0.5%	0.350%±0.02

Table 8: The flow parameters of drug powder observed

Parameter	Immediate Layer	Sustained Layer
Bulk density (gm/ml)	0.761	0.673
Tapped density (gm/ml)	0.894	0.831
Hausner's ratio	1.175	1.234
% Carr's index	14.8	19.01

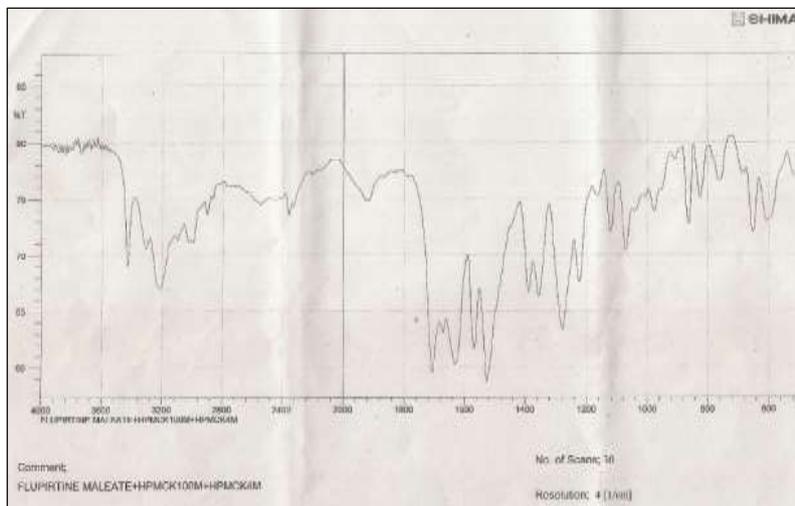


Fig 9: IR spectra of Drug

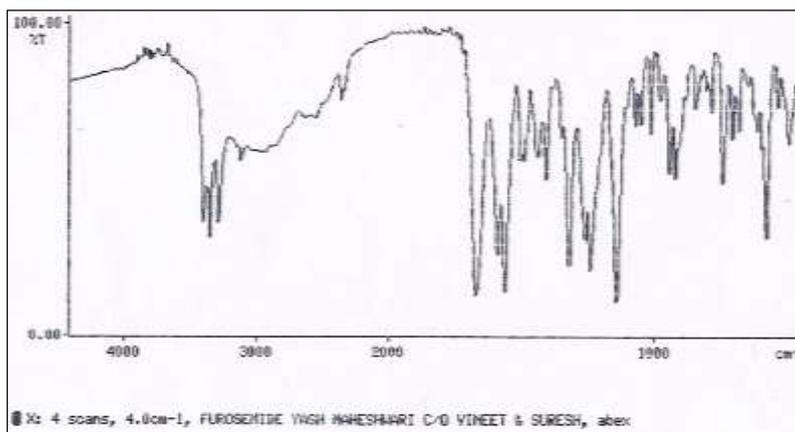


Fig 10: IR spectra of mixture of drug and excipient

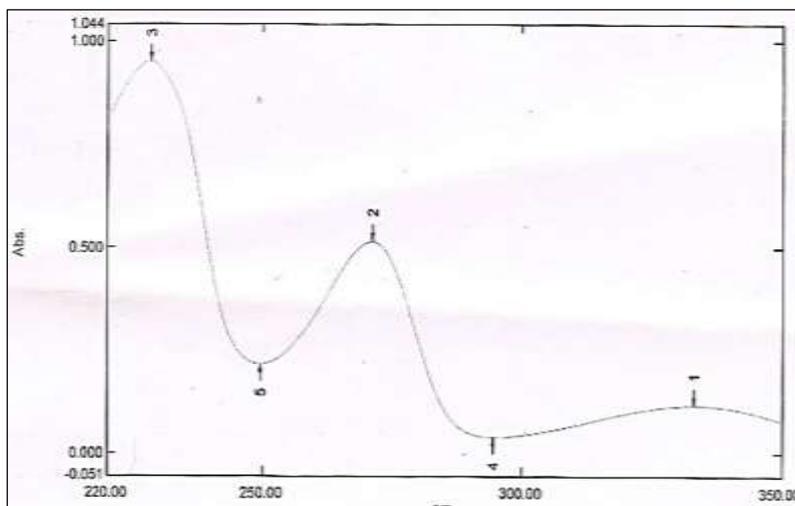


Fig 11: UV spectra of the sample drug

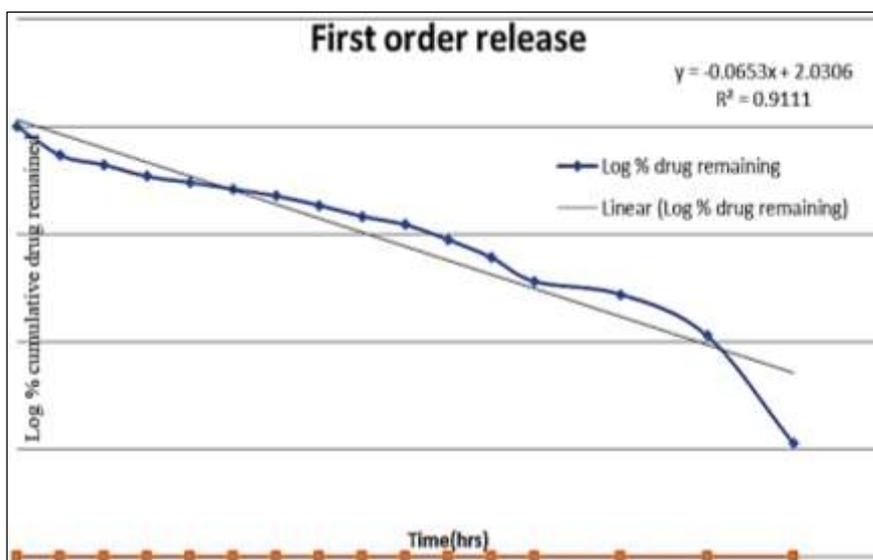


Fig 12: First order drug release model of the bilayer tablet formulation

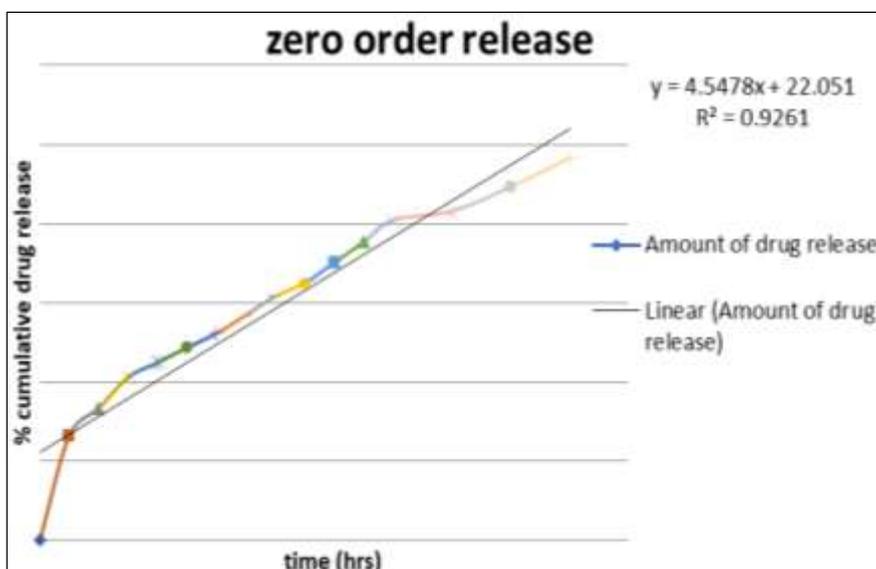


Fig 13: Zero order drug release model of the bilayer tablet formulation

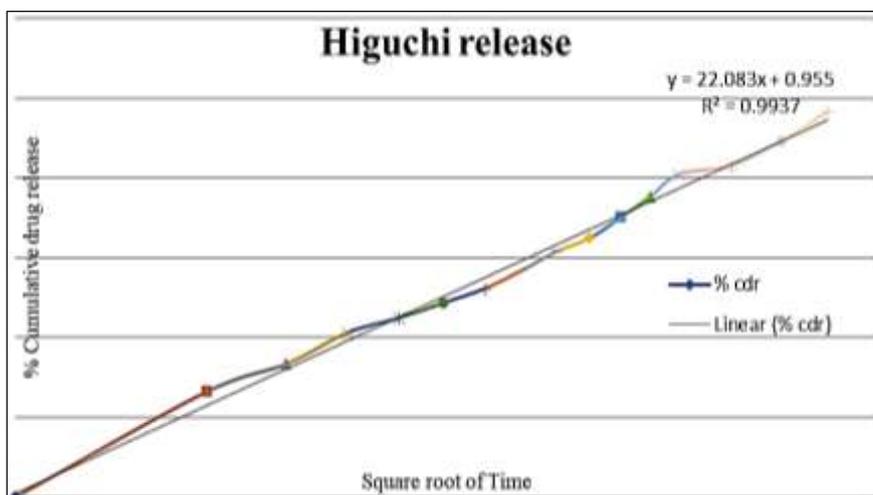


Fig 14: Higuchi drug release model of the bilayer tablet formulation

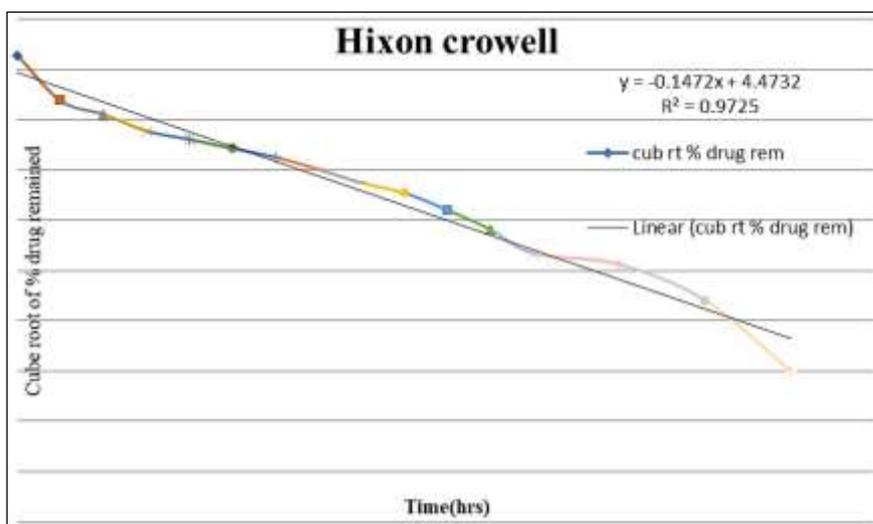


Fig 15: Hixon-Crowell model of the optimized formulation

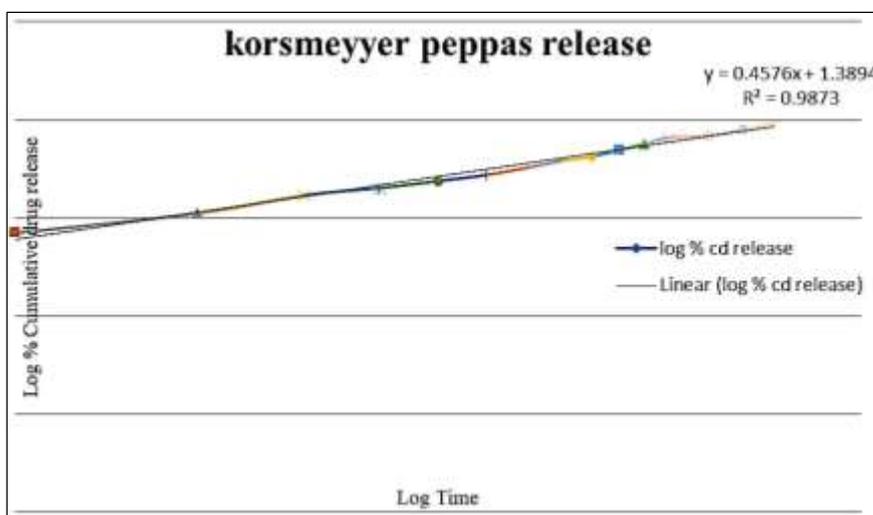


Fig 16: Korsmeyer-Peppas drug release model of the bilayer tablet formulation

Table 9: R² value of drug release kinetic models

S. No.	Model	R ²
1.	Zero order	0.926
2.	First order	0.911
3.	Higuchi	0.993
4.	Hixon-crowell	0.972
5.	Korsmeyer Peppas	0.987

Stability study of optimized formulation

Table 10: Stability study of bilayer tablet

Sr. No.	Parameters	Initial	After study
1	Hardness	4.8±0.31	4.9±0.15
2	Friability	0.48%±0.015	0.45±0.18
3	Disintegration time	1:2±0.12	1:1±0.16

Where all values are mean ± S.D. for n=3.

Table 11: Drug content study

S. No.	Parameters	Drug	Initial	After study
1.	Drug content	Sustained Clonidine layer	98.55%±1.18	96.68%±1.42
2.		Immediate Clonidine layer	98.40%±1.58	97.38%±1.32

Where all values are mean ± S.D. for n=3.

Table 12: Percentage cumulative drug release of Clonidine layer

Time (hr)	Drug release (Clonidine sustained layer)		
	Initial	After 15 days	After 30 days
0	0.00	0.00	0.00
1	10.25±0.08	10.07±0.11	10.03±0.08
2	10.79±0.05	10.55±0.19	10.65±0.04
3	21.69±1.16	20.94±2.18	20.58±1.96
4	26.19±0.07	25.43±1.07	25.20±0.95
5	32.60±1.04	31.84±0.04	31.29±0.93
6	37.73±0.07	36.97±1.07	36.67±0.93
7	42.22±1.04	41.46±0.04	40.97±0.82
8	51.19±0.07	50.43±1.07	49.81±1.05
9	56.96±0.07	56.20±1.07	55.77±0.94
10	60.81±0.07	60.05±1.07	59.68±0.93
11	67.22±1.04	66.46±0.04	66.35±0.15
12	73.63±1.17	70.92±3.94	70.97±3.99
14	79.40±1.17	77.99±2.38	77.99±4.10
16	88.37±2.28	78.64±2.18	78.34±1.99
18	93.50±0.07	82.48±2.18	81.93±1.90
20	94.78±1.17	87.61±3.29	87.25±3.05

Where all values are mean ± S.D. for n=3.

Table 13: Percentage of cumulative drug release of Clonidine layer

Time (min)	Drug release (Clonidine immediate layer)		
	Initial	After 15 days	After 30 days
0.00	0.00	0.00	0.00
5	42.22±0.52	40.84±0.80	41.01±0.12
10	52.85±1.19	50.09±0.64	50.04±0.63
15	62.38±0.88	60.14±0.81	60.14±0.12
20	77.22±0.67	74.78±0.86	74.75±0.06
25	82.56±1.11	78.43±0.81	78.47±0.25
30	86.50±0.38	84.58±0.52	84.40±0.12

Where all values are mean ± S.D. for n=3.

Discussion

On the basis of the above parameters, Bilayer tablet of (Clonidine) was found to be best, it was concluded that, Bilayer tablet of (Clonidine) was best.

Conclusion

The present study demonstrated the successful preparation of once daily conventional release bilayer tablet of clonidine. The project work entitled, formulation development, and optimization of clonidine bilayer tablet was carried out in the present study it was mainly concentrated on the optimization of the formulation based on compatibility study with DSC as well as some other parameters. The Optimized formulation S1 and S3 was studied for the drug content and in-vitro drug release. Tablet blends were evaluated for various parameters such as bulk density, tapped density, and tablets were evaluated for thickness, drug content, hardness, and weight variation. It was revealed that the tablets of all batches had acceptable physical parameters. In the present study clonidine 8, 200mg tablets have been formulated and developed using direct compression and dry granulation technique, to provide a safe, highly effective method for treating rheumatoid arthritis, pain and inflammation. While reducing undesirable adverse effects. Pre and post formulation parameters were studied for the formulated batches. The result of all the physical and *in vitro* dissolution data concluded that bilayer tablet (S3, I3) was the most promising formulation. The trial conducted with the consecutive three batches revealed relative standard deviation below 2%, indicative the insignificant batch-to-batch variation that can be overcome if processes are

run out in a controlled manner. Clonidine using microcrystalline cellulose, corn starch blend would be cost effective and dissolution mediums 0.1N HCl and pH 6.8 buffer would be the ideal media for conducting dissolution studies. Stability study was carried out for the optimized formulation according to ICH guidelines at 40±2 °C/ 75±5% RH for 1 month. Tablets were evaluated for assay disintegrating time, *in vitro* drug release profile after one month. The results showed that there was no significant change in the physical and chemical parameters of the tablet, hence the formulation was found to be stable. It was concluded that the bilayer tablet formulation can act as a better tool for the successful administration of two or more drugs which will remain stable for a longer period of time.

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